



TCACGTAAAA AGGTATCTA GAATTATGAT GATTACTCTG CGCAAACTTC CTCTGGCGGT TGCCGTGCGA GCGGGCGTAA TGTCTGCTCA GGCCATGGCC
AGTGCATTTT TCCCATAGAT CTTAATACTA CTAATGAGAC GCGTTTGAAG GAGACCGCCA ACGGCAGCGT CGCCCGCATTT ACAGACGAGT CCGGTACCGG
MetMe tileThrLeu ArgLysLeup roLeuAlava lAlaValAla AlaGlyValM etSerAlaGl nAlaMetAla
^Start of lamB signal sequence

GGTCCCGAAA CTCTGTGGG TGCTGAACTG GTTGACGCTC TGCAGTTTCGT ATGTGGTGAT CGAGGCTTCC TGTTCAACAA ACCGACTGGG GCTGGATCCT
CCAGGGCTTT GAGACAGCC ACGACTTGAC CAAGTGGAG ACGTCAAGCA TACACCACTA GCTCCGAAGG ACAAGTTGTT TGGCTGACCC CGACCTAGGA
GlyProGluT hrLeuCysGl yAlaGluLeu ValAspAlaL euGlnPheVa lCysGlyAsp ArgGlyPheL euPheAsnLy sProThrGly AlaGlySerSer
^Start of IGF-I (Y24L, Y31A)

CCTCTCGTCG TGCTCCCCAG ACTGGTATTG TTGACGAATG CTGCTTTTCGT TCTTGGGACC TGCGTCGTCT GGAAATGTAT TGGCTTCCCC TGAACCCCGC
GGAGAGCAGC ACGAGGGGTC TGACCATAAC AACTGCTTAC GACGAAAGCA AGAAGCTGG ACGCAGCAGA CCTTTACATA ACGCGAGGGG ACTTTGGGCG
SerArgAr gAlaProGln ThrGlyIleV alAspGluCy sCysPheArg SerCysAspL euArgArgLe uGluMetTyr CysAlaProL eulysProAla

TAAATCTGCT TAGAAGCTCC TAACGCTCGG TTGCCGCCCGG GCGTTTTTTTA TTGTTAACTC ATGTTTGACA GCTTATCATC GATAAGCTTT AATGCGGTAG
ATTTAGACGA ATCTTCGAGG ATTGCGAGCC AACGGCGGCC CGCAAAAAAT AACAAATTGAG TACAAACTGT CGAATAGTAG CTATTGAAA TTACGCCCATC
LysSerAla Am*

Nucleotide and Amino Acid Sequence of the LamB Signal Sequence and IGF-I (Y24L, Y31A)

FIG. 1

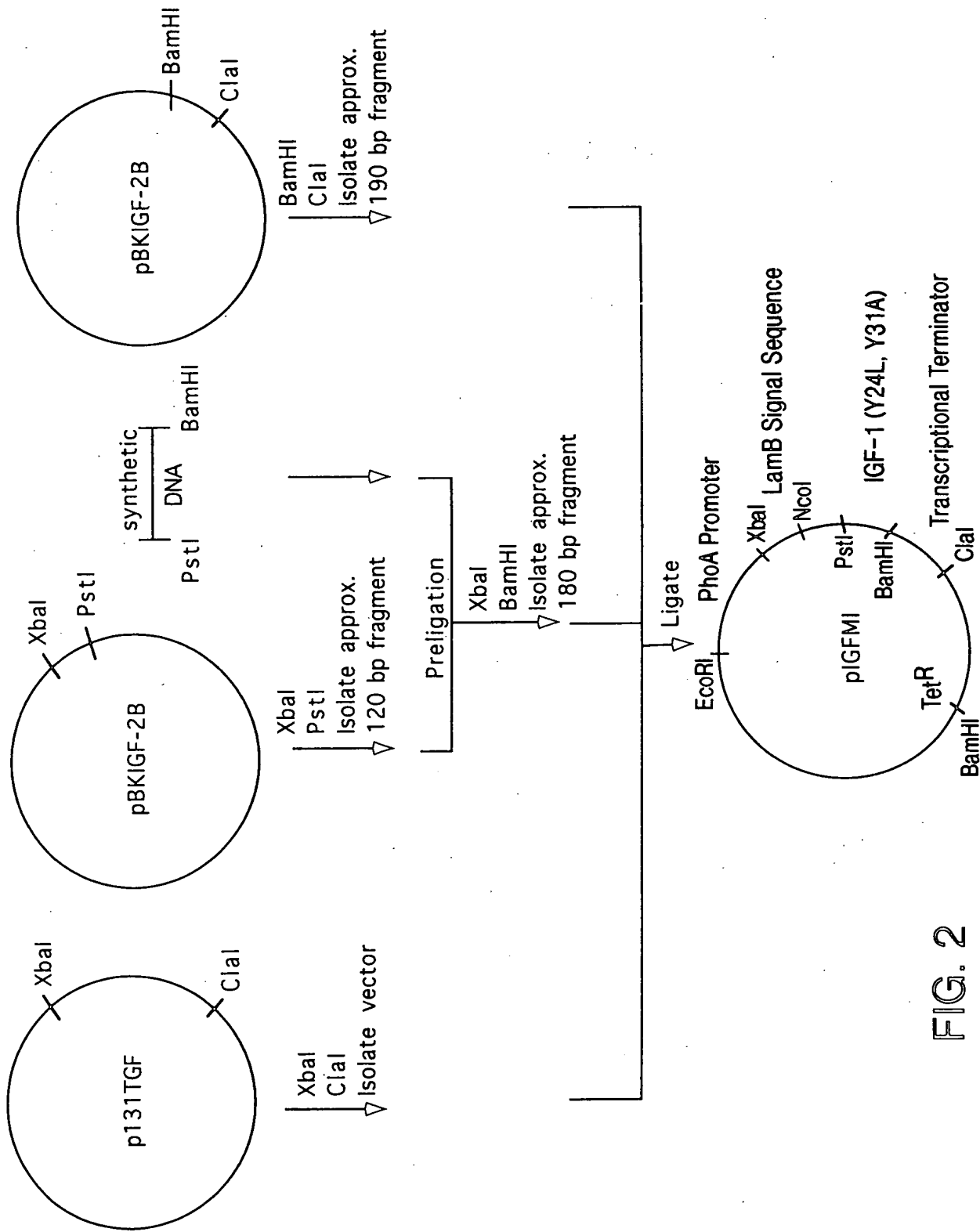


FIG. 2





plasmid IGFMI

length: 5115 (circular)

1 GAATTCAACT TCTCCATACT TTGGATAAGG AAATACAGAC ATGAAAAATC TCATTGCTGA GTTGTATTATTT AAGCTTGCCC AAAAAAGAAGA AGAGTCGAAT
CTTAAGTTGA AGAGGTATGA AACCTATTCC TTATATGCTG TACTTTTAG AGTAACGACT CAACAATAAA TTTTCTTCT TCTCAGCTTA

101 GAACTGTGTG CGCAGGTAGA AGCTTTGGAG ATTATCGTCA CTGCAATGCT TCGCAATATG GCGCAAAATG ACCAACACGG GTTGATTGAT CAGGTAGAGG
CTTGACACAC GCGTCCATCT TCGAAACCTC TAATAGCAGT GAGGTTACGA AGCGTTATAC CCGGTTTTAC TGGTTGTGCG CAACTAACTA GTCCATCTCC

201 GGGCGCTGTA CGAGGTAAG CCCGATGCCA GCATTCCCTGA CGACGATACG GAGCTGCTGC GCGATTACGT AAAGAAGTTA TTGAAGCATC CTCGTCAGTA
CCCCGCACAT GCTCCATTTC GGGCTACGGT CATAAGGACT GCTGCTATGC CTCGACGACG CGCTAATGCA TTTCTTCAAT AACTTCGTAG GAGCAGTCAT

301 AAAAGTTAAT CTTTTCACAA GCTGTCAATAA AGTTGTCACG GCCGAGACTT ATAGTCGCTT TGTTTTTTATT TTTTAATGTA TTTGTAACATA GTACGCAAGT
TTTTCAATTA GAAAAGTTGT CGACAGTATT TCAACAGTGC CCGCTCTGAA TATCAGCGAA ACAAAAATAA AAAATTACAT AAACATTGAT CATCGGTTCA

401 TCACGTAAAA AGGGTATCTA GAATTATGAT GATTACTCTG CGCAAACTTC CTCTGGCGGT TGCCGTCGCA GCGGGCGTAA TGCTGCTCA GGCCATGGCC
AGTGCAATTT TCCCATAGAT CTTAATACTA CTAATGAGAC GCGTTTGAAG GAGACCGCA ACAGCAGCGT CGCCCGCAT ACAGACGAGT CCGGTACCGG
1 MetMe ttleThrLeu ArgLysLeuP roLeuAlaValAla AlaGlyValM etSerAlaG1 nAlaMetAla

501 GGTCGCCGAAA CTCGTGCGG TGCTGAACCTG GTTGACGCTC TGCACTTCGT ATGTGGTGAT CGAGGCTTCC TGTTCACAA ACCGACTGGG GCTGGATCCT
CCAGGCTTT GAGACACGCC ACAGCTTGAC CAAGCTTGAC ACCTGCTTAC GACCAAGCA TACACCATA TACCCGAAAG ACAAGTTGTT TGGCTGACCC CGACTAGGA

26 GlyProGluT hrLeuCysG1 yAlaGluLeu ValAspAlaL euGlnPheVa lCysGlyAsp ArgGlyPheL euPheAsnLy sProThrGly AlaGlySerSer

601 CCTCTCGTCG TGCTCCCCAG ACTGGTATTG TTGACGAATG CTGCTTTCGT TCTTGCAGC TCGCTGCTCT GGAATGTAT TCGCTCCCC TGAACCCCGC
GGAGAGCAGC ACGAGGGGTC TGACCATTAAC AACTGCTTAC GACCAAGCA AGAACGCTGG ACGCAGCAGA CCTTTACATA ACGCAGGGG ACTTTGGGCG

60 SerArgAr gAlaProGln ThrGlyIleV alaSpGluCy sCysPheArg SerCysAspL euArgArgLe uGluMetTyr CysAlaProL euLysProAla

701 TAAATCTGCT TAGAAGCTCC TAACGCTCGG TTGCCGCGCG GCGTTTTTTA TTGTTAACTC ATGTTTGACA GCTTATCATC GATAAGCTTT AATGCGGTAG
ATTTAGACGA ATCTTCGAGG ATTGCGAGCC AACGGCGGCC CGCAAAAAAT AACAATTGAG TACAAACTGT CGAATAGTAG CTATTGAAA TTACGCCATC

93 LysSerAla Am*

801 TTTATCACAG TTAAATTGCT AACGCAGTCA GGCACCGTGT ATGAAATCTA ACAATGCGCT CATCGTCATC CTCGGCACCG TCACCTTGA TGCTGTAGGC
AAATAGTCTC AATTTAACGA TTGCGTCAGT CCGTGGGACA TACTTTAGT TGTACCGCA GTAGCAGTAG GAGCCGTGGC AGTGGACCT ACGACATCCG

901 ATAGGCTGG TTATGCCGT ACTGCCGGC CTCTTGGGG ATATCGTCCA TTCCGACAGC ATCGCCAGTC ACTATGGCGT GCTGTAGCG CTATATGCGT
TATCCGAACC AATACGGCCA TGACGGCCCG GAGAACGCC TATAGCAGGT AAGCTGTCTG TAGCGGTCTG TAGATCCGCA CGACGATCGC GATATACGCA

1001 TGATGCAATT TCTATGCGCA CCCGTTCTCG GAGCACTGTC CGACCGCTTT GCGCGCGGCC CAGTCTCTGT CGCTTCGCTA CTTGGAGCCA CTATCGACTA
ACTACGTTAA AGATACGCGT GGGCAAGAGC CTCGTGACAG GCTGGCGAAA CCGCGGCGG GTCAGGACGA GCGAAGCGAT GAACCTCGGT GATAGCTGAT

FIG. 3A



1101 CGCATCATG GCGACCACAC CCGTCTCTGT GATCCTCTAC GCCGGACGCA TCGTGGCCGG CATCACCCGG GCCACAGGTG CGTTGCTGG CGCCTATATC
GCGCTAGTAC CGCTGGTGTG GCGAGGACAC CTAGGAGATG CCGCCTGCGT AGCACCCGGC GTAGTGGCCG CCGTGTCCAC GCCAACGACC GCGGATATAG

1201 GCCGACATCA CCGATGGGGA AGATCGGGCT CGCCACTTCG GGTCTATGAG CGCTGTGTTT GCGTGGGTA TGGTGGCAGG CCCCCTGGCC GGGGACTGT
CGGCTGTAGT GGCTACCCCT TCTAGCCCGA GCGGTGAAGC CCGAGTACTC CCGAACAAAG CCGACCCAT ACCACCGTCC GGGGACCCG CCCCCTGACA

1301 TGGGGCCCAT CTCCTTGCAT GCACCATTC CCGGCGGGC TTGCGCGGGC GGTCTCAAC GGTCTCAACC TACTACTGG CTGCTTCTTA ATGCAGGAGT CGCATAAGG
ACCCGCGGTA GAGGAACGTA CGTGGTAAG AACGCCCGC CACGAGTTG CCGGAGTTG ATGATGACC GACGAAGAT TACGTCTCTA GCGTATTCCC

1401 AGAGCTCGA CCGATGCCCT TGAGAGCCTT CAACCCAGTC AGCTCCTTCC GGTGGGCGG GGCATGACT ATCGTCGCC CACTTATGAC TGTCTTCTT
TCTCGAGCT GGCTACGGGA ACTCTCGGA GTTGGGTGAG TCGAGGAAG CCACCCGCGC CCCGTACTGA TAGCAGCGG GTGAATCTG ACAGAAGAAA

1501 ATCATGCAAC TCGTAGGACA GGTGCCGGCA GCGCTCTGG CCGTCTTCCG CGAGGACCG GTCCTGGG AAAGCGACCT CCGCTGCTA CTAGCCGGAC AGCGAACGCC
TAGTACCTG AGCATCCTGT CCACGGCCGT CCGGAGACCC AGTAAAGCC GCTCCTGGG AAAGCGACCT CCGCTGCTA CTAGCCGGAC AGCGAACGCC

1601 TATTCGGAAT CTTGCACGCC CTCGCTCAAG CCTTCGTAC CTTTCGGC ACCAACGTT TCGGCGAGAA GCAGGCCATT ATCGCCGGCA TGGCGGCCGA
ATAAGCCTTA GAACGTGCGG GACGAGTTC GGAAGCAGTG ACCAGGCGG TGGTTTGCAA AGCCGCTCTT CGTCCGGTAA TAGCGGCCGT ACCGCCGGCT

1701 CGCGCTGGC TAGTCTTGC TGGCGTTCG GACGCGAGC TGGATGGCT TCCCCATTAT GATTCCTTC GCTTCGGCG GCATCGGGAT GCCCGCGTTG
GCGGACCCG ATGCAGACG ACCGCAAGC CTGCGCTCG ACCTACCGA AGGGTAATA CTAAGAAGAG CGAAGGCCG CGTAGCCCTA CGGGCGCAAC

1801 CAGGCCATGC TGTCCAGGCA GGTAGATGAC GACCATCAGG GACAGCTTCA AGGATCGTC CCGGCTCTTA CCAGCCTAAC TTCGATCACT GGACCGCTGA
GTCCGGTAGG ACAGGTCCGT CCATCTACTG CTGGTAGTCC CTGTGGAAGT TCCTAGCGAG CCGCGAGAAT GGTGGATTG AAGCTAGTGA CCTGGCGACT

1901 TCGTCACGGC GATTTATGCC GCCTCGGCGA GCACATGGA GCGGTGGA TGGATTGTAG GCGCCGCCCT ATACCTTGT TGCCTCCCG CGTTGCGTGC
AGCAGTGCCG CTAATACGG CCGAGCCGT CCGTACCTT GCGCAACCGT ACCTAACATC CCGCGCGGA TATGGAACAG ACGGAGGGG GCAACGCAGC

2001 CGGTGCATGG AGCCGGGCA CTCGACCTG AATGGAAGC GCGGACCTT CGCTAACGGA TTCACCACTC CAAGAATTGG AGCCAATCAA TTCTTGGGA
GCCACGTACC TCGGCCCGGT GGAGCTGGAC TTACCTTCGG CCGCGTGGG GCGATTGCTT AAGTGGTGA GTTCTTAACC TCGGTTAGTT AAGAAGCCT

2101 GAACTGTGAA TGGCAAAACC AACCTTGGC AGAATATATC CATCGCGTCC GCCATCTCCA GCAGCCGCAC GCGCGCATC TCGGGCAGCG TTGGGTCTTG
CTTGACACTT ACGGCTTGG TTGGGAACCG TCTTGTATAG GTAGCGCAGG CCGTAGAGGT CCGCGCGTG CCGCGCGTAG AGCCCGTCCG AACCCAGGAC

2201 GCCACGGGTG CGCATGATCG TGCTCTGTG GTTGAAGAC CCGTACCTGG CAACCTCTGG CCGGTAGGCT GCGCGGGTGG CCTTACTGGT TAGCAGAATG AATCACCGAT ACGCGAGCGA
CGGTGCCAC GCGTACTAGC ACGAGGACAG CAACCTCTGG CCGCATCCGA CCGCCCCAAC GGAATGACCA ATCGTCTTAC TTAGTGGCTA TCGGCTCGCT

2301 ACGTGAAGCG ACTGCTGTG CAAAACGTCT GCGACCTGAG CAACAACATG AATGCTCTT GGTTCCTGT TTTGTAAG TCTGGAACG CGGAAGTCTG
TGCACTTCCG TGACGACGAC GTTTTGAGA CGCTGGACTC GTTGTGTAC TTACCAGAAG CCAAGGCAC AAGCATTTT AGACCTTTTC GCCTTCAGTC

2401 CGCCCTGCAC CATATGTTT CCGATCTGCA TCGCAGGATG CTGCTGGCTA CCCTGTGGA CACCTACATC TGTATTAACG AAGCGCTGGC ATTGACCCCTG
GCGGACGCTG GTATACAAAG GCCTAGACGT AGCGTCTAC GACGACCGAT GGGACACCTT GTGGATGTAG ACATAATTG TTCCGACCG TAACTGGAC

FIG. 3B



2501 AGTGATTTT CTCTGGTCCC GCCGCATCCA TACCGCCAGT TGTTTACCT CACAACGTT CAGTAACCGG GCATGTTTCAI CATCAGTAAC CCGTATCGTG
TCACTAAAAA GAGACCAGGG CGCGTAGGT ATGGCGGTCA ACAATGGGA GTGTTGCAAG GTCATTGGCC CGTACAAGTA GTAGTCATTG GGCATAGCAC

2601 AGCATCTCT CTCGTTTCAT CCGTATCAAT ACCCCCATGA ACAGAAATTC CCCCTTACAC GGAGGCATCA AGTGACCAAA CAGGAAAAAA CCGCCCTTAA
TCGTAGGAGA GAGCAAAGTA GCCATAGTAA TGGGGGTACT TGTCTTTAAG GGGGAATGTG CCTCCGTAGT TCACTGGTTT GTCCTTTTTT GCGGGGAATT

2701 CATGGCCCG TTTATCAGAA GCCAGACATT AACGCTTCTG GAGAAACTCA ACGAGCTGGA CCGCGATGAA CAGGCAGACA TCTGTGAATC GCTTCACGAC
GTACCGGCG AATAGTCTT CCGTCTGTAA TTGGAAGAC CTCTTTGAGT TGCTCGACCT GCGCTACTT GTCCGTCTGT AGACACTTAG CGAAGTGCTG

2801 CACGCTCATG AGCTTTACCG CAGCTGCCTC GCGGTTTCG GTGATGACGG TGAAAACCTC TGACACATGC AGTCCCCGA GACGGTCACA GCTTGTCTGT
GTGCGACTAC TCGAAATGGC GTCGACGGAG CCGCAAAAGC CACTACTGCC ACTTTGGAG ACTGTGTACG TCGAGGGCCT CTGCGAGTGT CGAACAGACA

2901 AAGCGGATGC CGGGAGCAGA CAAGCCCCTC AGGCGCGTC AGCGGTGTT GCGGGGTGTC GGGCGGAGC CATGACCCAG TCACGTAGCG ATAGCGGAGT
TTGCGCTACG GCCCTCGTCT GTTCGGGAG TCCCGGCGAG TCGCCACAA CCGCCACAG CCCCGGTG GTACTGGTC AGTGCATCGC TATCGCCTCA

3001 GTATACTGC TTAACATATG GGCATCAGAG CAGATTGTAC TGAGAGTGCA CCATATGCGG TGTGAAATAC CGCACAGATG CGTAAGGAGA AAATACCGCA
CATATGACCG AATTGATACG CCGTAGTCTC GTCTACATG ACTCTCACGT GGTATACGCC ACACCTTTATG CCGTGTCTAC GCATTCTCT TTTATGGCGT

3101 TCAGGCGTTC TTCCGCTTCC TCGCTCACTG ACTCGTTCGG CTCGGTCTGT GAGCGGTATC AGTCACTCA AAGCGGTAA TACGGTTATC
AGTCCGCGAG AAGCGAAGG ACGAGTGAC TGAGCGACGC GAGCCAGCAA GCCGACCGG CTCGCCATAG TCGAGTGTG TTTCCGCCATT ATGCCAATAG

3201 CACAGAATCA GGGATAACG CAGGAAGAA CATGTGAGCA AAAGGCCAGC AAAAGGCCAG GAACCGTAAA AAGGCCGCT TGCTGGCGCT TTTCCATAGG
GTGTCTTAGT CCCCTATTGC GTCCCTTCTT GTACACTCT GTTCCGGTGC TTTTCCGGTC CTTGGCATTT TTCCGGCGCA ACGACCGCAA AAAGGTATCC

3301 CTCGCGCCCC CTGACGAGCA TCACAAAAAT CGACGCTCAA GTCAGAGGTG GCGAAACCCG ACAGGACTAT AAAGATACCA GCGCTTTCCC CCTGGAAGCT
GAGGCGGGGG GACTGCTCGT AGTGTTTTTA GCTGGAGTT CAGTCTCCAC CCGTTTGGC TGTCTGATA TTTCTATGGT CCGCAAAGGG GGACCTTCGA

3401 CCCTCGTGG CTCTCCTGTT CCGACCCCTGC CGCTTACCGG ATACCTGTCC GCCTTTCTCC CTTCGGGAAG CGTGGCGCTT TCTCATAGCT CACGCTGTAG
GGGAGCACGC GAGAGGACAA GGCTGGGACG GCGAATGGCC TATGGACAGG CCGAAAGAGG GAAGCCCTTC GCACCGCGAA AGAGTATCGA GTGCGACATC

3501 GTATCTCAGT TCGGTGTAGG TCGTTCGCTC CAAGCTGGGC TGTGTGCACG AACCCCGCT TCAGCCCGAC CCGTGGCCT TATCCGGTAA CTATCGTCTT
CATAGAGTCA AGCCACATCC AGCAAGCGAG GTTCGACCCG ACACACGTGC TTGGGGGGCA AGTCGGGCTG CGCACCGGA ATAGGCCATT GATAGCAGAA

3601 GAGTCCAACC CCGTAAGACA CGACTTATCG CCACTGGCAG CAGCCACTGG TAACAGGATT AGCAGAGCGA GGTATGTAGG CCGTGTACA GAGTCTTGA
CTCAGGTTGG GCCATTCTGT GCTGAATAGC GGTGACCGTC GTGGGTGACC ATTGTCTTAA TCGTCTCGCT CCATACATCC GCCACGATGT CTCAAGAACT

3701 AGTGGTGGC TAACTACGGC TACACTAGAA GGACAGTATT TGGTATCTGC GCTCTGTGA AGCCAGTTAC AGCCGAAAA AGAGTTGGTA GCTCTTGATC
TCACCACCGG ATTGATGCCG ATGTGATCTT CCTGTCTATA ACCATAGACG CGAGACGACT TCGGTCAATG GAAGCCTTTT TCTCAACCAT CGAGAACTAG

FIG. 3C



3801 CGGCAACAA ACCACCGCTG GTAGCGGTGG TTTTGTGTT TGCAAGCAGC AGATTACGCG CAGAAAAAAA GGATCTCAAG AAGATCCTTT GATCTTTCT
GCCGTTGTT TGGTGGCGAC CATCGCCACC AAAAAACAA ACGTTGCTG TCTAATGCGC GTCTTTTTT CCTAGAGTTC TTCTAGGAAA CTAGAAAAA
3901 ACGGGTCTG ACGCTCAGTG GAACGAAAAAC TCACGTTAAG GGATTTTGGT CATGAGATTA TCAAAAAGGA TCTTCACCTA GATCCTTTTA AATTAATAAT
TGCCCCAGAC TCGGAGTCAC CTTGCTTTTG AGTGCAATTC CCTAAAACCA GTACTCTAAT AGTTTTTCTT AGAAGTGGAT CTAGGAAAAAT TTAATTTT
4001 GAAGTTTAA ATCAATCTAA AGTATATATG AGTAAACTTG GTCTGACAGT TACCAATGCT TAATCACTGA GGCACCTATC TCAGCGATCT GTCTATTTCTG
CTTCAAAAT TAGTTAGAT TCATATATAC TCATTTGAAC CAGACTGTCA ATGGTTACGA ATTAGTCACT CCGTGGATAG AGTCGCTAGA CAGATAAAGC
4101 TTCAATCCATA GTTGCTGAC TCCCCGTCGT GTAGATAACT ACGATAAGGG AGGGCTTACC ATCTGGCCCC AGTGCTGCAA TGATACCGCG AGACCCACGC
AAGTAGGTAT CAACGGACTG AGGGGCAGCA CATCTATTGA TGCTATGCCC TCCCGAATGG TAGACCGGGG TCACGACGTT ACTATGGCGC TCTGGGTGCG
4201 TCACCGGCTC CAGATTTATC AGCAATAAAC CAGCCAGCGG GAAGGGCCGA GCGCAGAAAT GGTCTGCAA CTTTATCCGC CTCCATCCAG TCTATTAAT
AGTGGCCGAG GTCTAAATAG TCGTTATTG GTCGGTGCGC CTTCCCGGCT CCGCTCTTCA CCAGGACGTT GAAATAGGCG GAGGTAGGTC AGATAATTAA
4301 GTTGCCGGA AGCTAGAGTA AGTAGTTCGC CAGTTAATAG TTTGCGCAAC GTTGTGCCC AATGCTGAG CATCGTGGT TCACGCTCGT CGTTTGGTAT
CAACGGCCCT TCGATCTCAT TCATCAAGCG GTCAATTATC AAACGCGTTG CAACAACGGT AACGACGTC GTAGCACCC AGTGCGAGCA GCACCAACATA
4401 GGCTTCTTC AGCTCCGGT CCCAACGATC AAGCGGAGT ACATGATCCC CCATGTTGTG CAAAAAAGCG GTTAGCTCCT TCGGTCTCTCC GATCGTTGTC
CCGAAGTAAG TCGAGGCCAA GGGTGTCTAG TTCCGCTCAA TGACTAGGG GGTACAACAC GTTTTTTCG CAATCGAGGA AGCCAGGAGG CTAGCAACAG
4501 AGAAGTAAGT TGGCCGAGT GTTATCACTC ATGGTTATGG CAGCACTGCA TAATTTCTCTT ACTGTCATGC CATCCGTAAG ATGCTTTTCT GTGACTGGTG
TCTTCTATCA ACCGGCTCA CAATAGTGAG TACCAATACC GTCGTGACGT ATTAAGAGAA TGACAGTACG GTAGGCATTC TACGAAAAA CACTGACCAC
4601 AGTACTCAAC CAAGTCATTC TGAGAATAGT GTATGCGGCG ACCGAGTTGC TCTTGCCCGG CGTCAACACG GGATAATACC GCGCCACATA GCAGAACTTT
TCATGAGTTG GTTCAGTAAG ACTCTTATCA CATAAGCGCG TGGCTCAACG AGAACGGGCG GCAGTTGTG CCTATTATGG CCGGTGTAT CGTCTTGAAA
4701 AAAAGTGCTC ATCATTTGAA AACGTTCTTC GGGGCGAAAA CTCTCAAGGA TCTTTACCGCT GTTGAGATCC AGTTGATGT AACCCACTCG TGCACCCCAAC
TTTTACAGG TAGTAACCTT TTGCAAGAA CCCCCTTTT GAGAGTCTCT AGAATGCGCA CAACTCTAGG TCAAGCTACA TTGGGTGAGC ACGTGGGTG
4801 TGATCTTCAG CATCTTTTAC TTTCACCAGC GTTCTGGGT GAGCAAAAAAC AGGAAGGCAA AATGCCGCAA AAGGGGAAAT AAGGGCGACA CGGAAATGTT
ACTAGAAGTC GTAGAAAATG AAGTGCTCG CAAAGACCCA CTCGTTTTTG TCCTTCCGTT TTACGGCGGT TTTTCCCTTA TTCCCGCTGT GCCTTTACAA
4901 GAATACTCAT ACTCTTCTCT TTTCAATATT ATTGAAGCAT TTATCAGGT TATTGCTCTCA TGAGCGGATA CATATTTGAA TGTATTTAGA AAAATAAACA
CTTATGAGTA TGAGAAGGAA AAGTTATAA TAACCTCGTA AATAGTCCCA ATAACAGAGT ACTCGCTAT GTATAAACTT ACATAAATCT TTTTATTGT
5001 AATAGGGGT CCGCGCACAT TTCCCCGAAA AGTGCCACCT GACGTCTAAG AAACCATTTAT TATCATGACA TTAACCTATA AAAATAGGCG TATCACGAGG
TTATCCCCAA GCGCGTGTA AAGGGGCTTT TCACGGTGGA CTGAGATTC TTTGGTAATA ATAGTACTGT AATTGATAT TTTTATCCGC ATAGTGCTCC
5101 CCCTTTCGTC TTCAA
GGGAAGCAG AAGTT

FIG. 3D

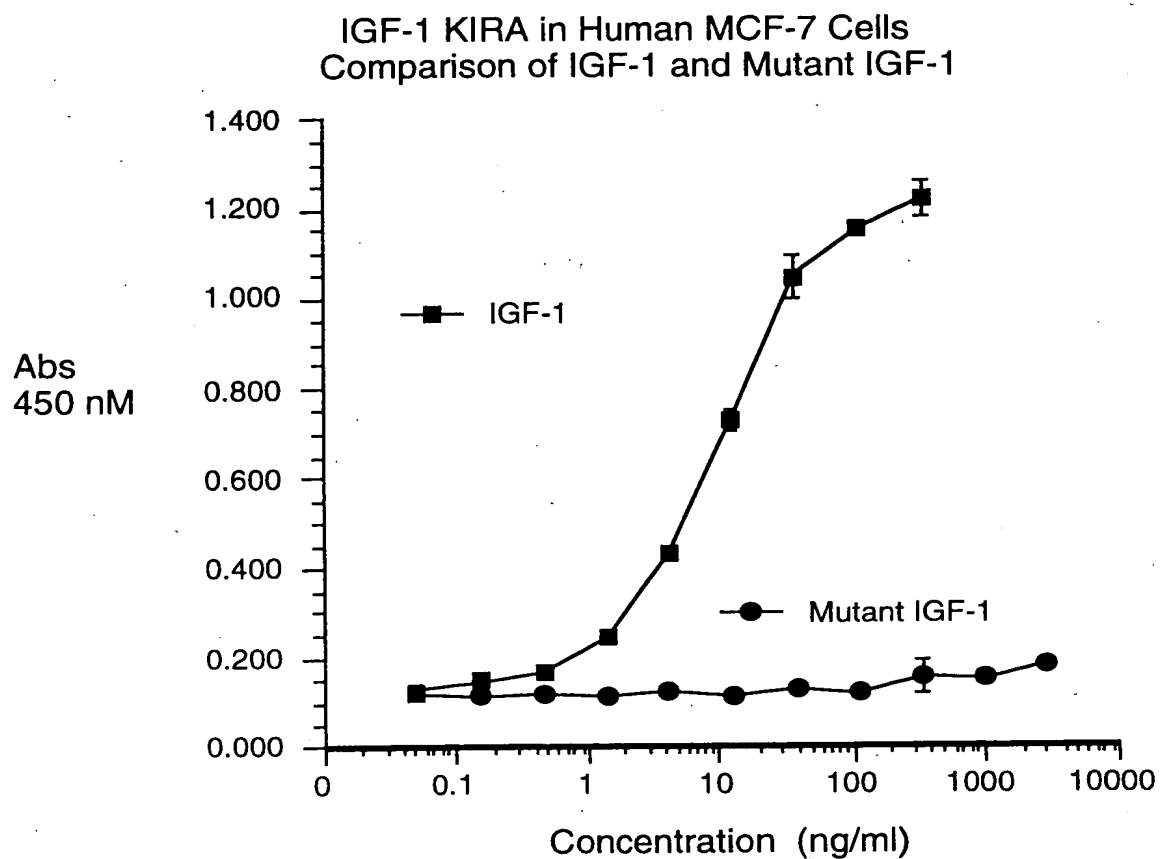


FIG. 4



IGF-1 (Leu²⁴ Ala³¹) is Inactive In Vitro

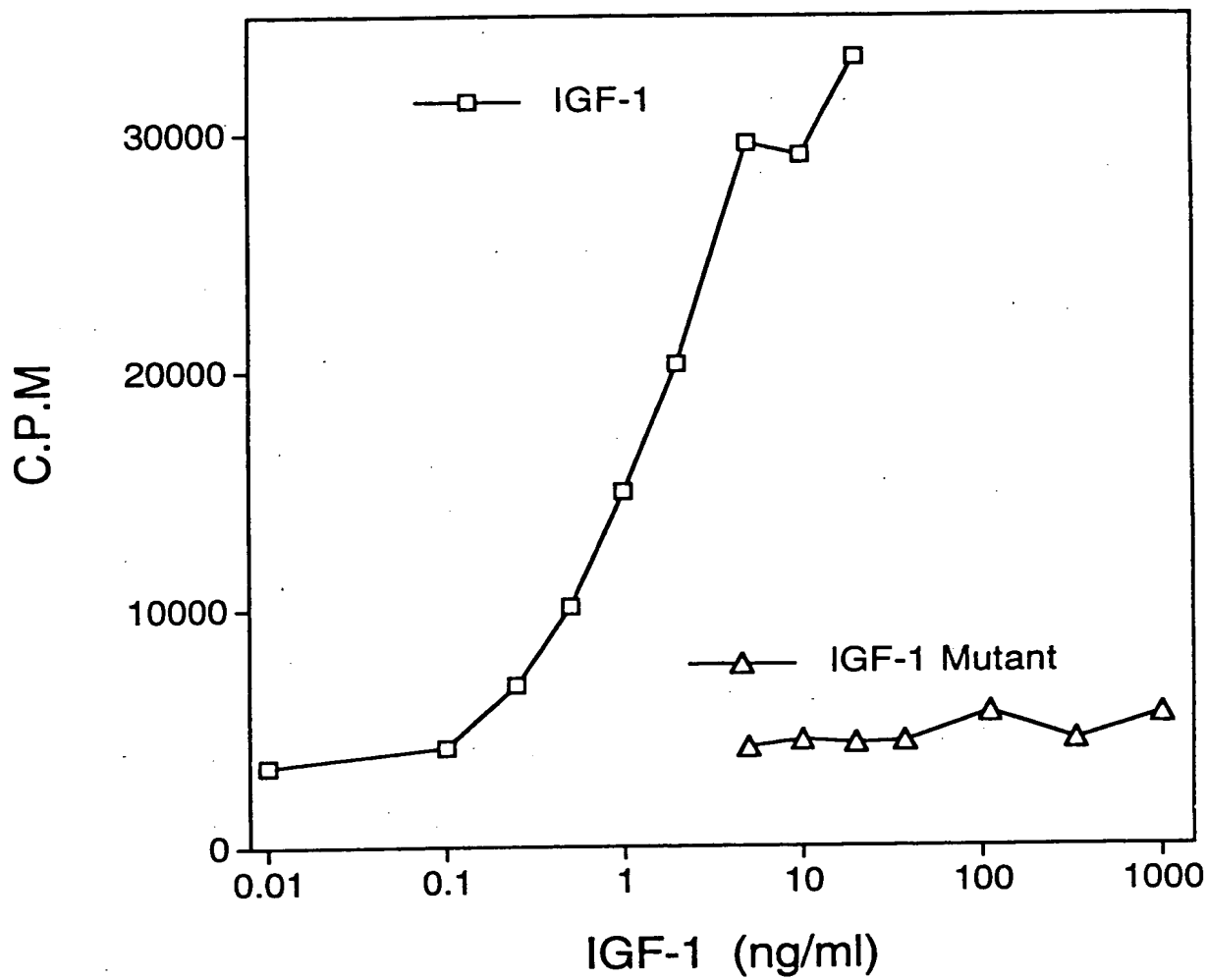


FIG. 5



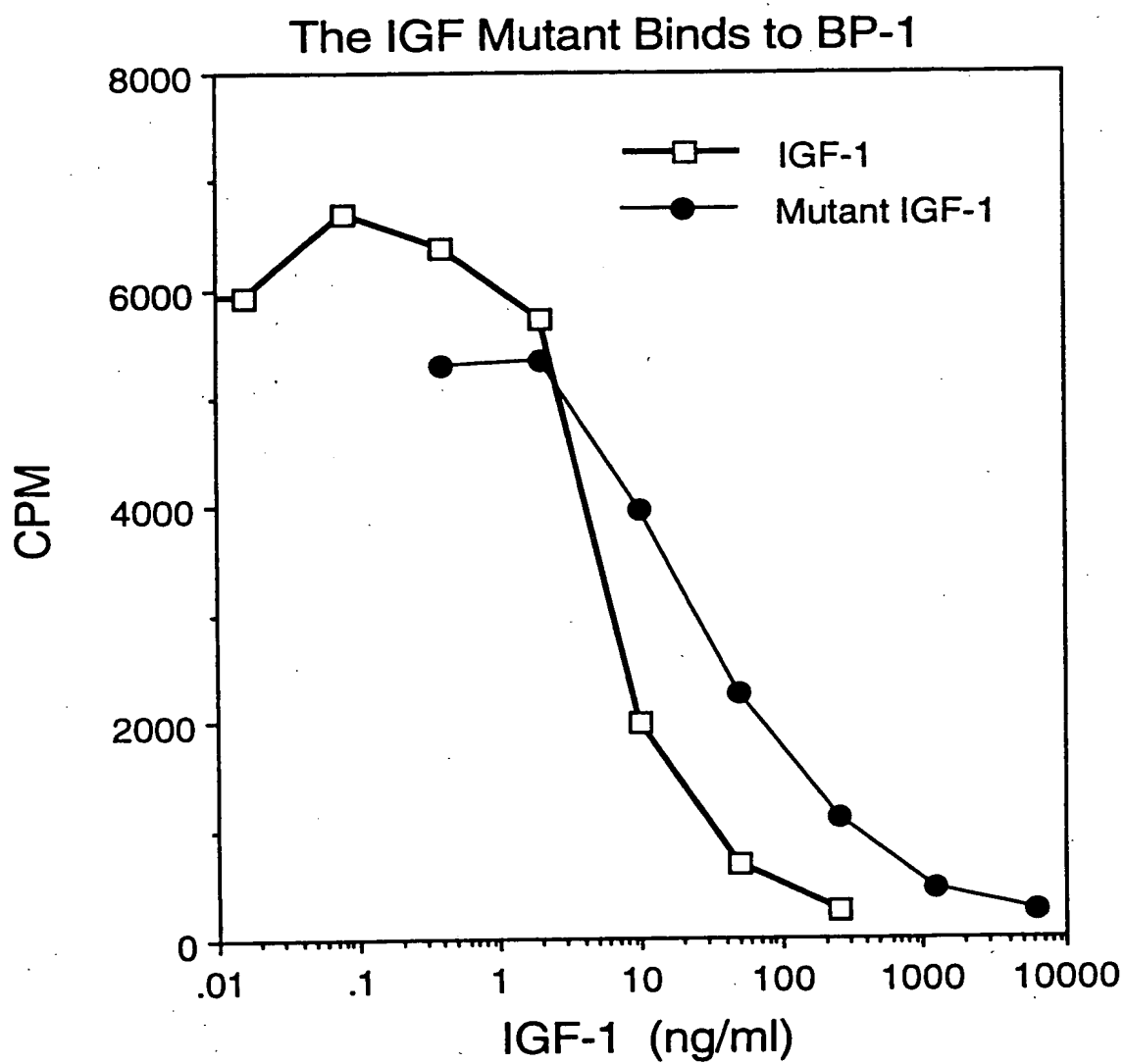
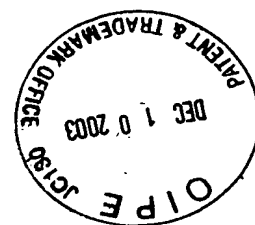


FIG. 6



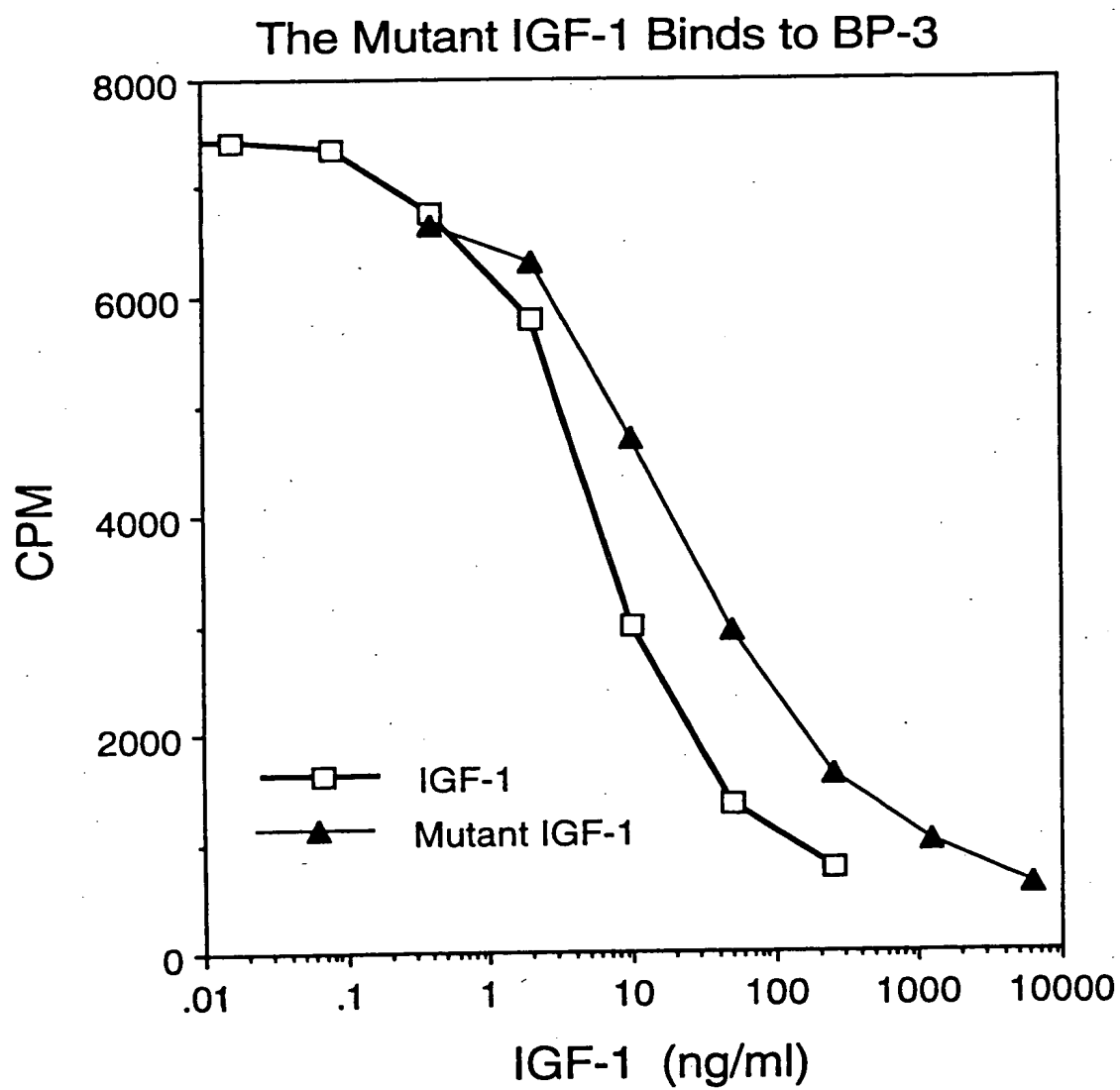
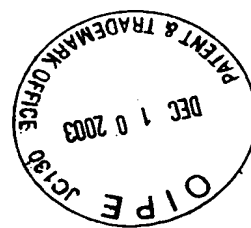


FIG. 7



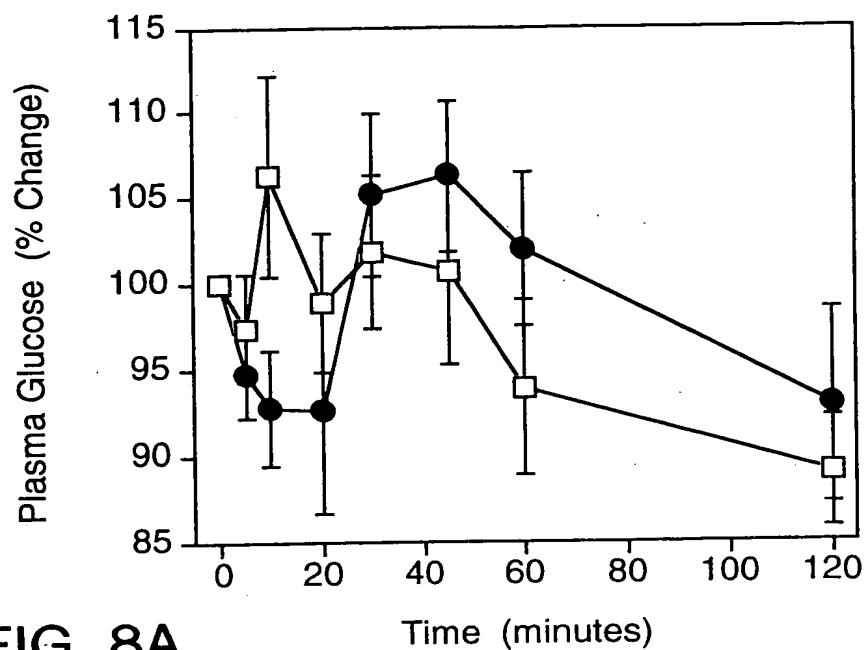


FIG. 8A

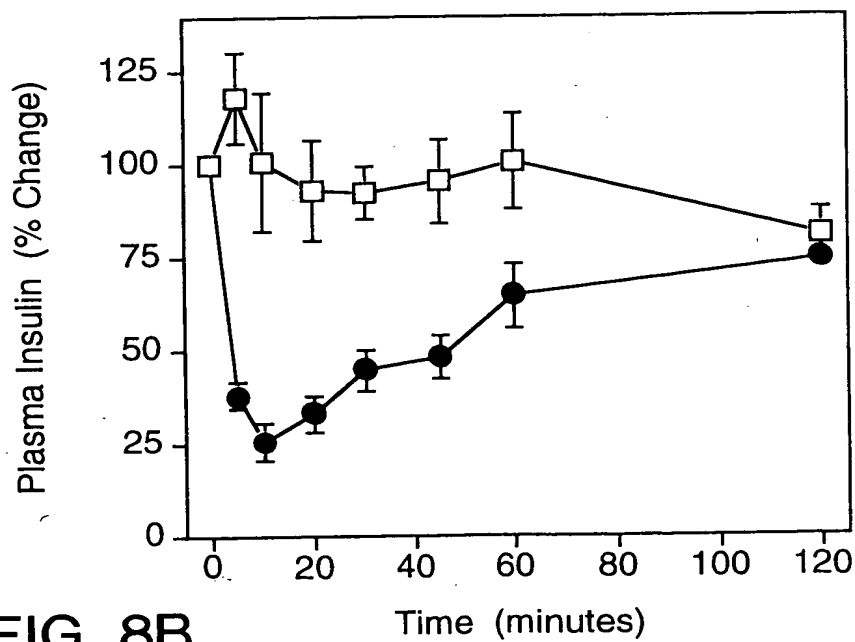


FIG. 8B

—□— Control —●— IGF-Mutant



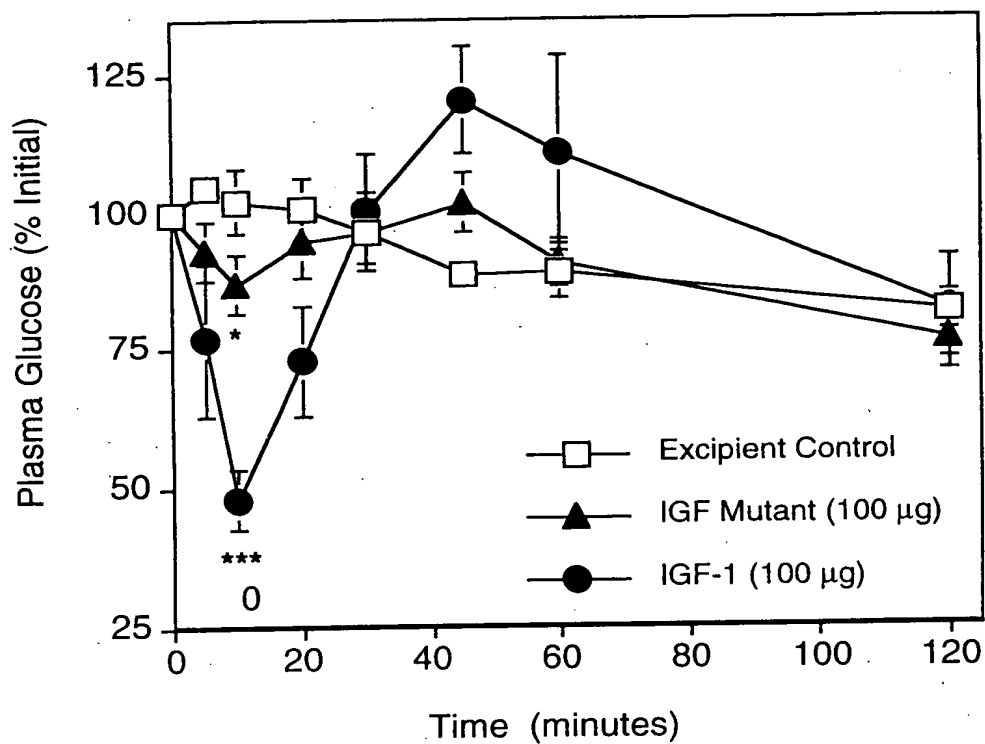


FIG. 9A

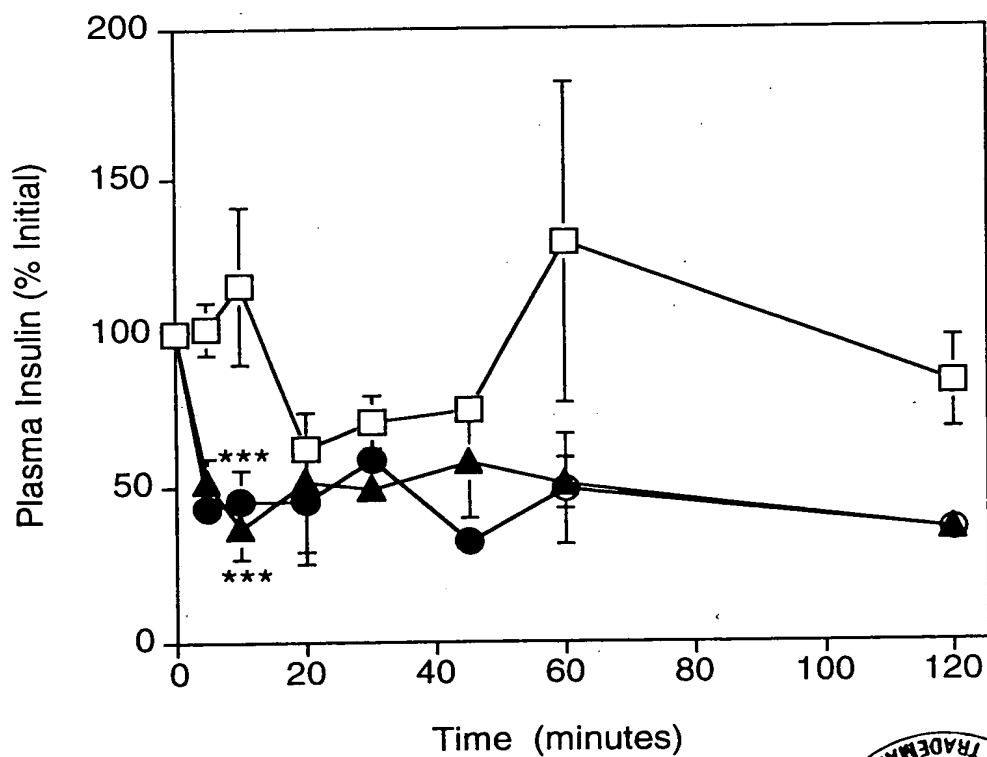
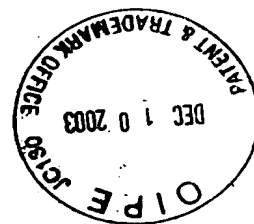


FIG. 9B



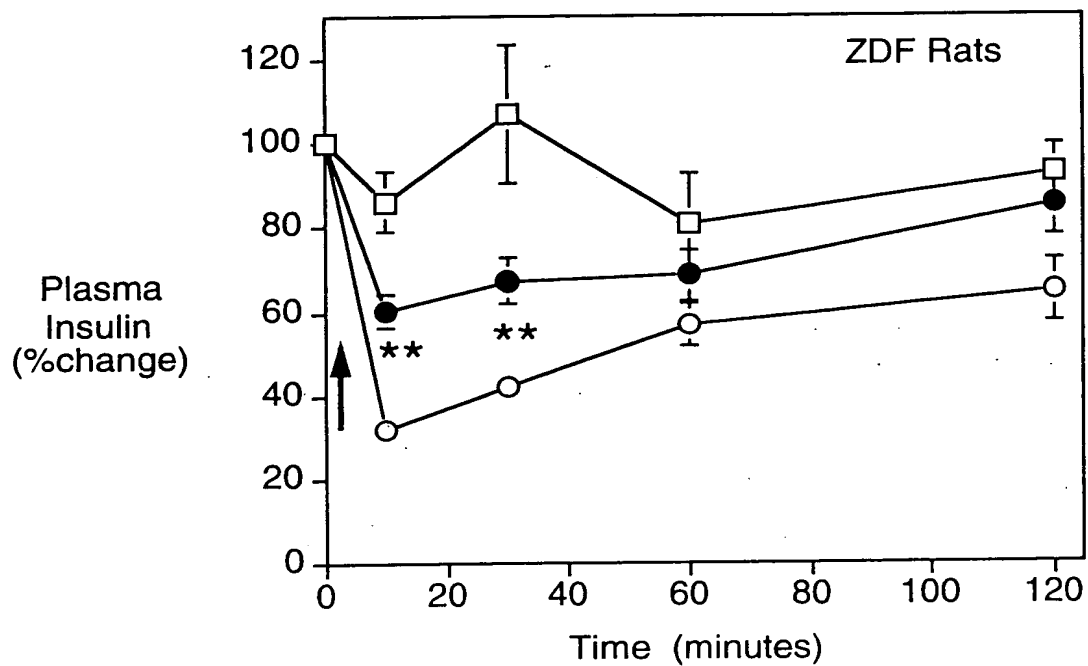


FIG. 10A

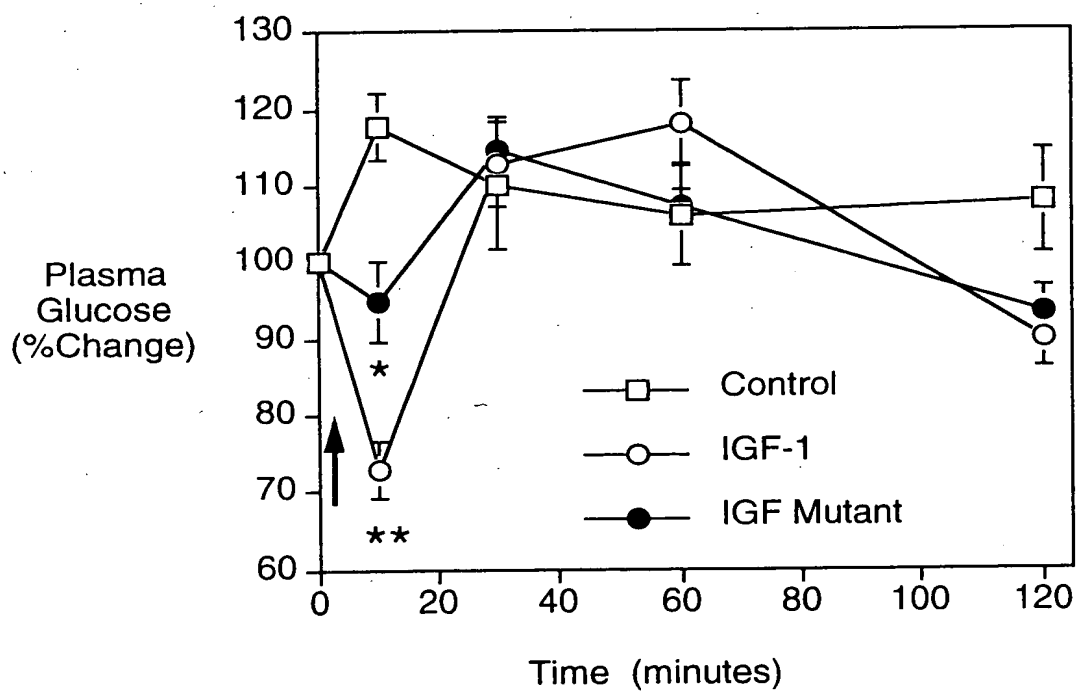
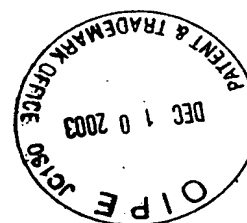


FIG. 10B



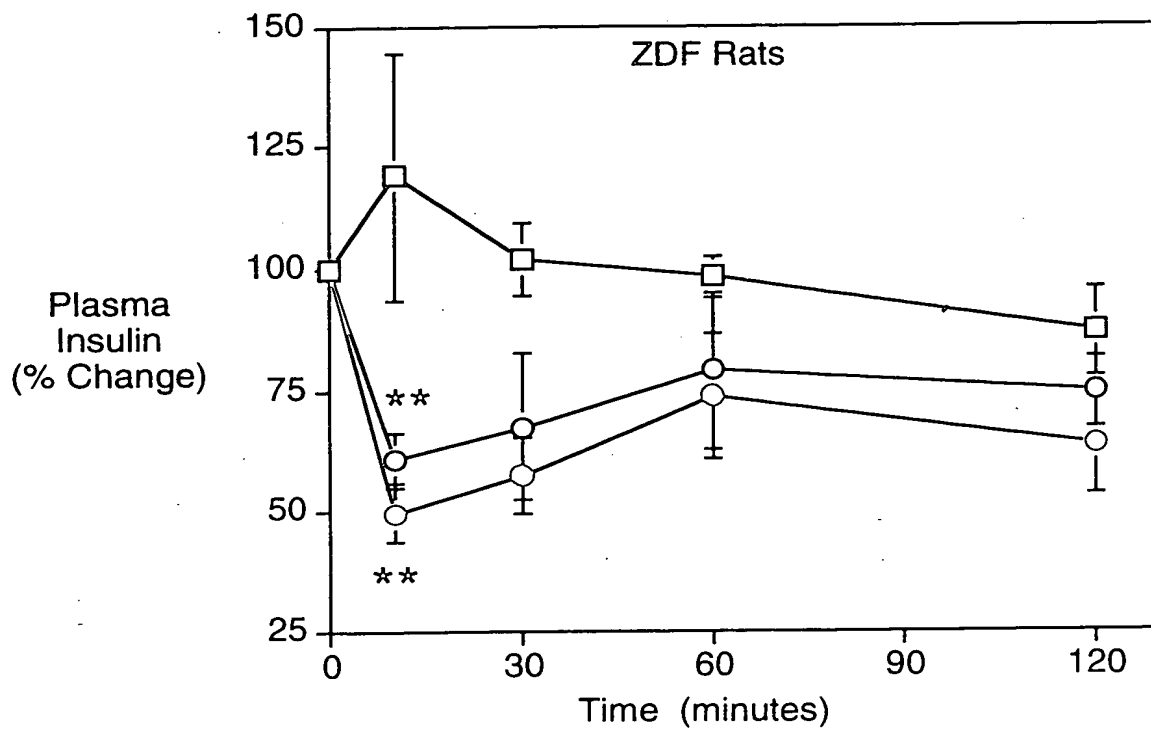


FIG. 11A

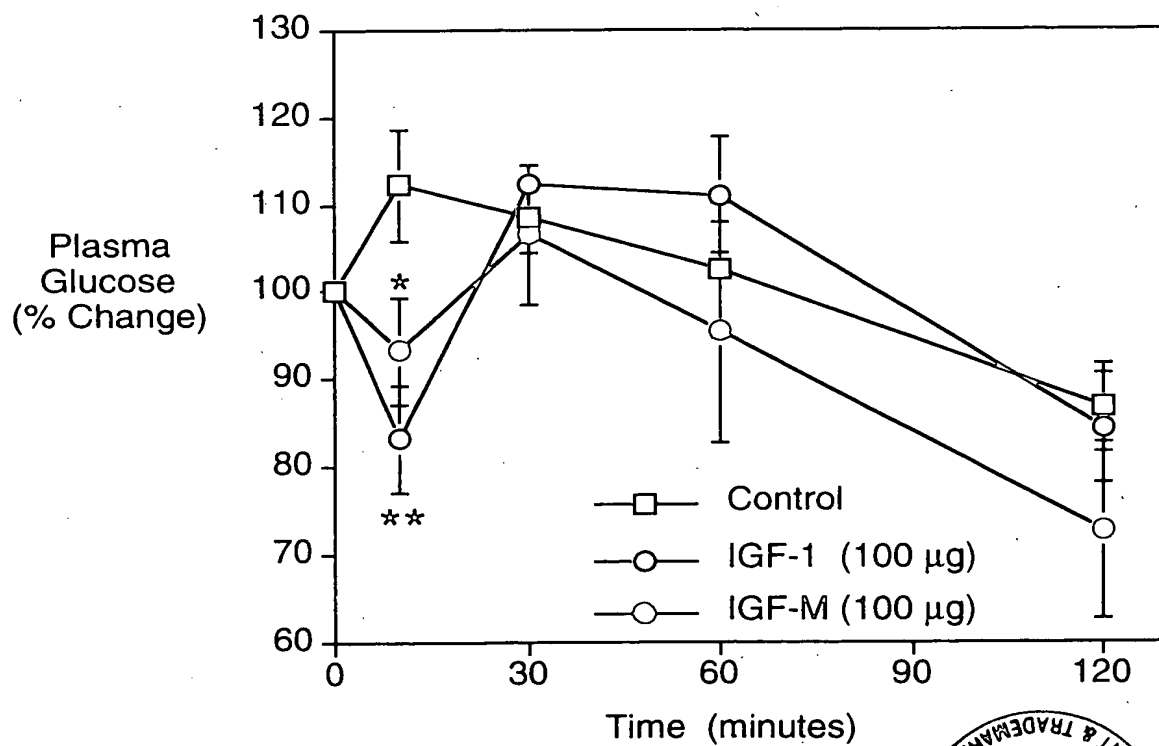
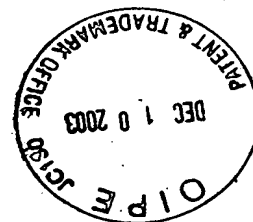


FIG. 11B



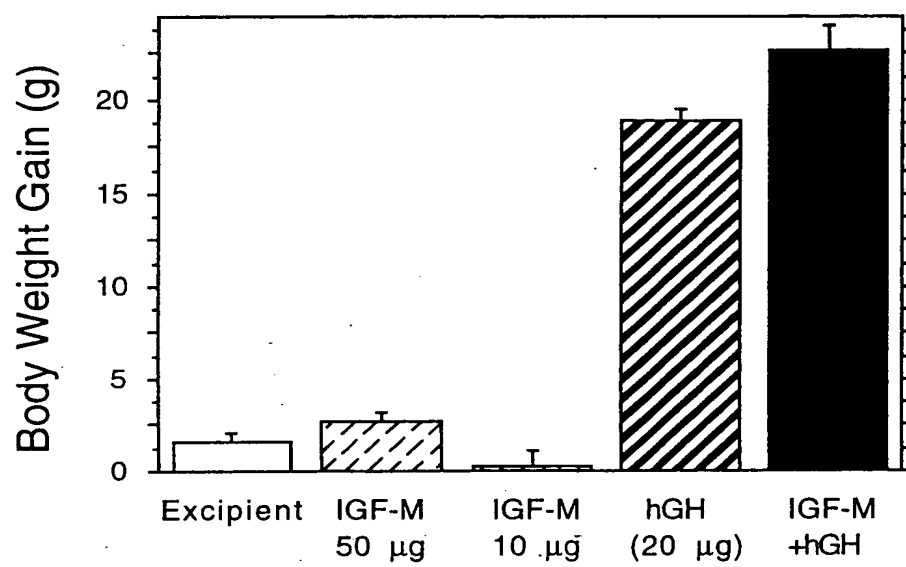
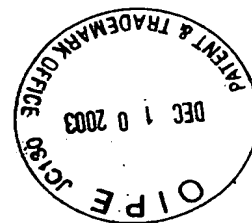


FIG. 12



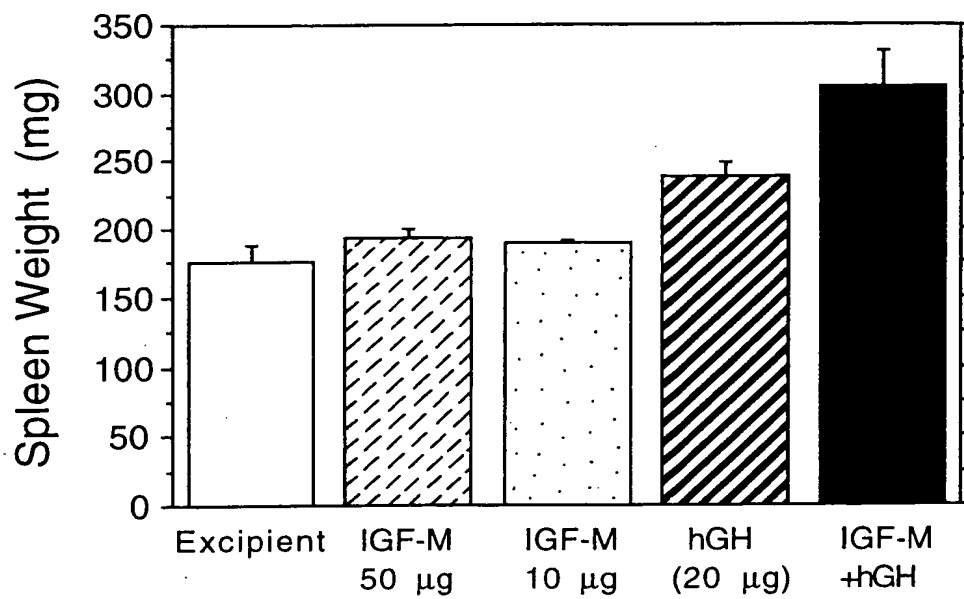


FIG. 13A

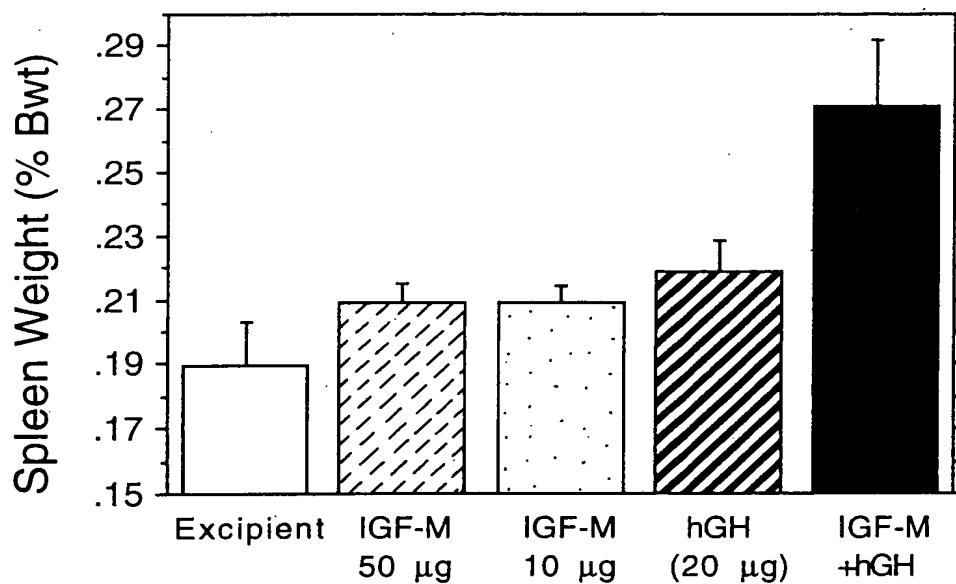
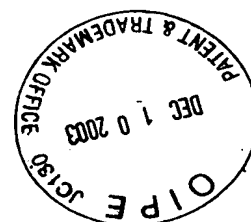


FIG. 13B



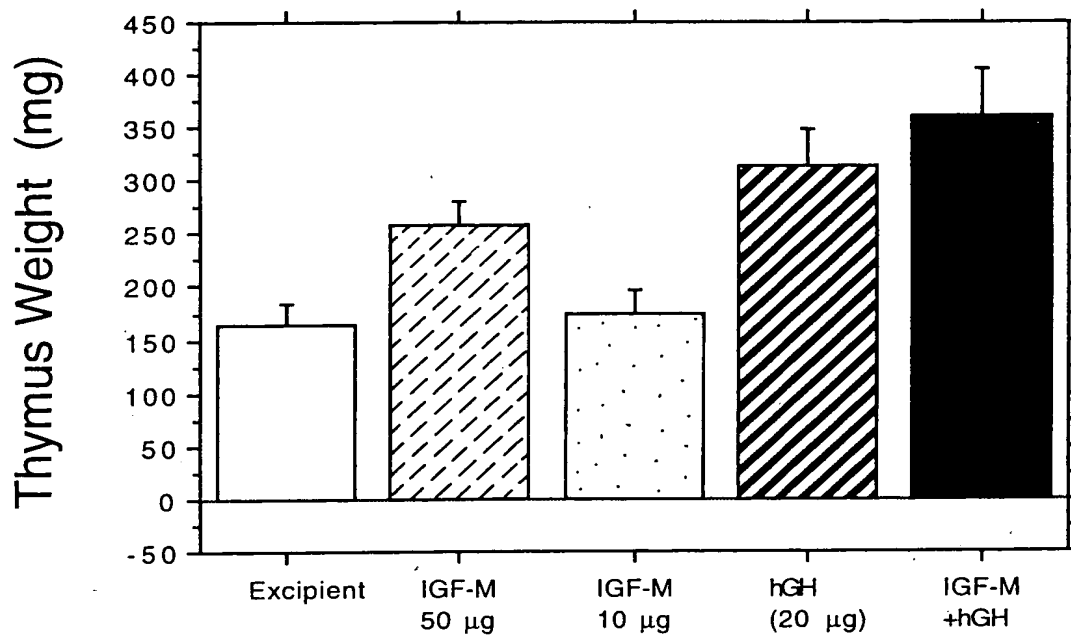


FIG. 14A

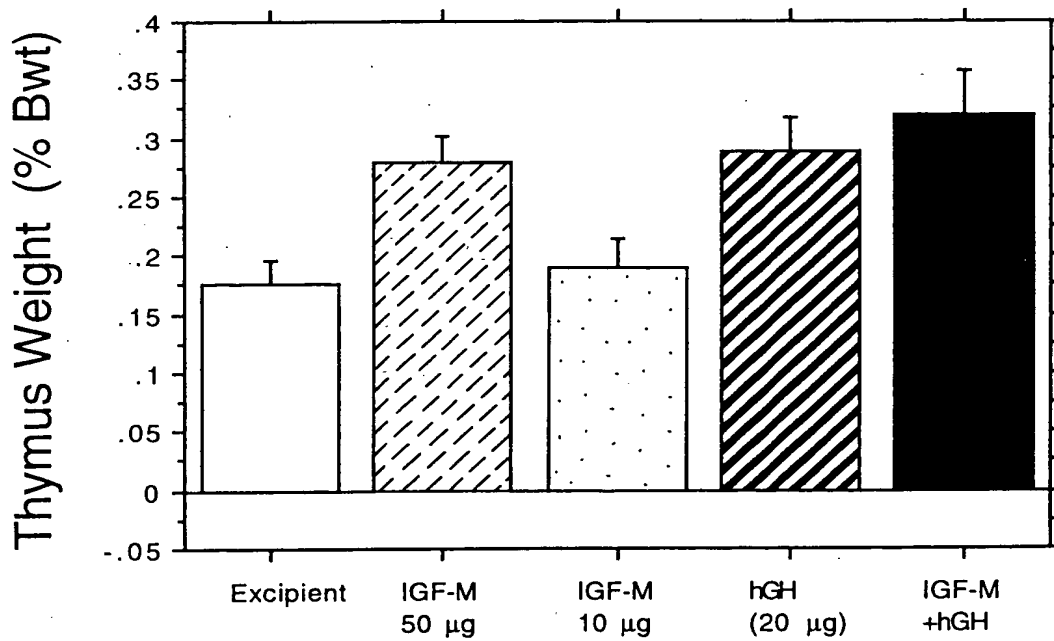
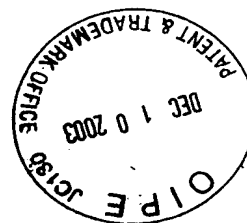


FIG. 14B



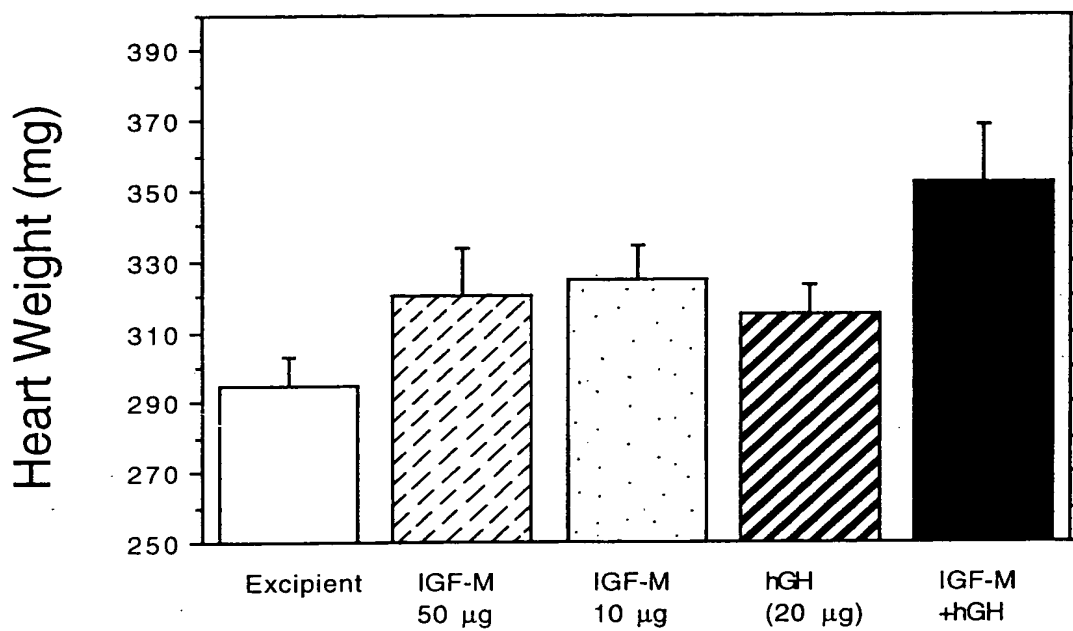


FIG. 15A

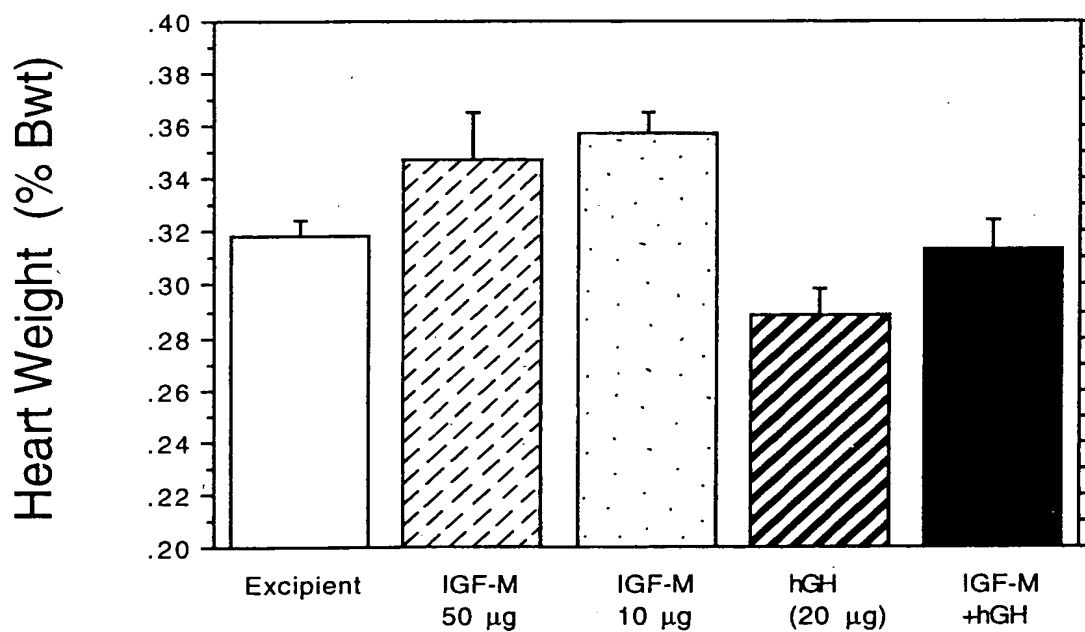
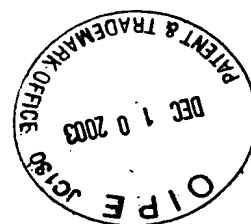


FIG. 15B



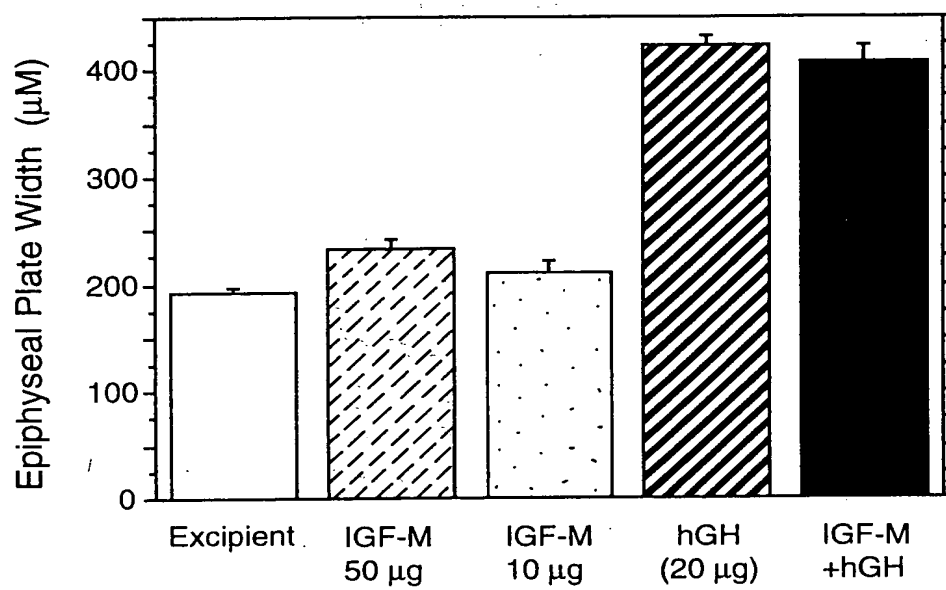
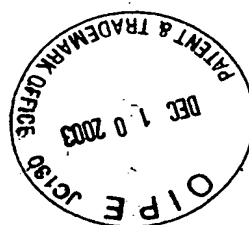


FIG. 16



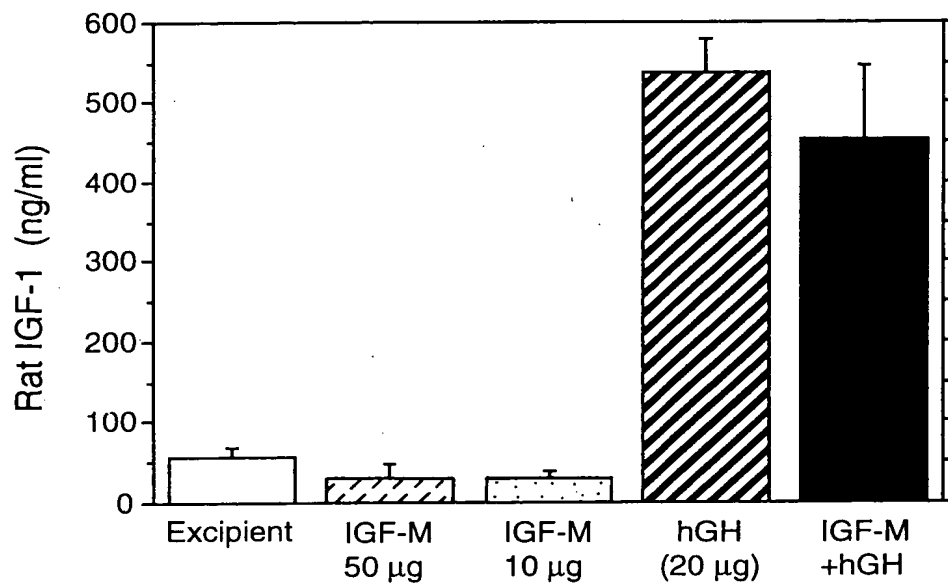


FIG. 17A

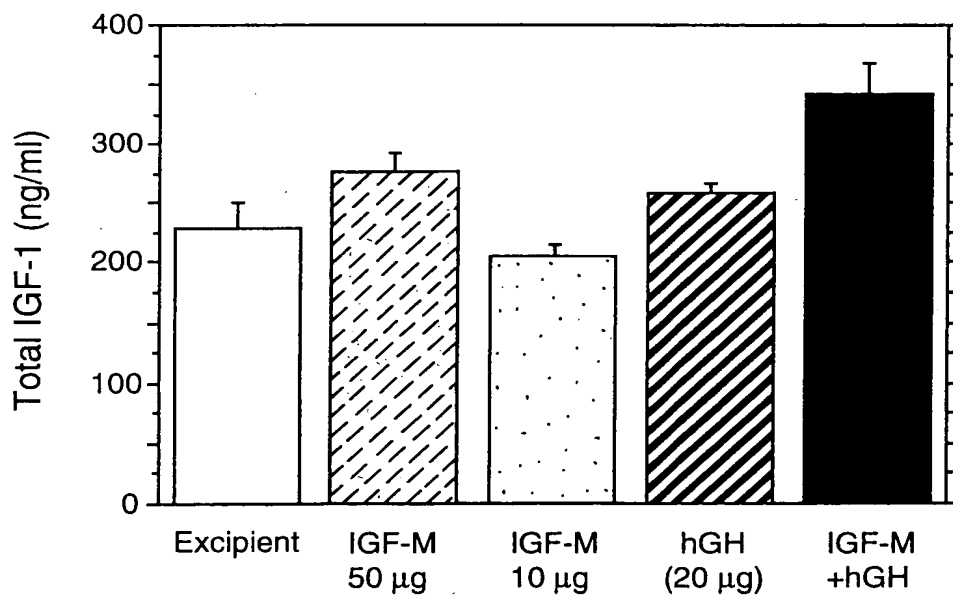


FIG. 17B



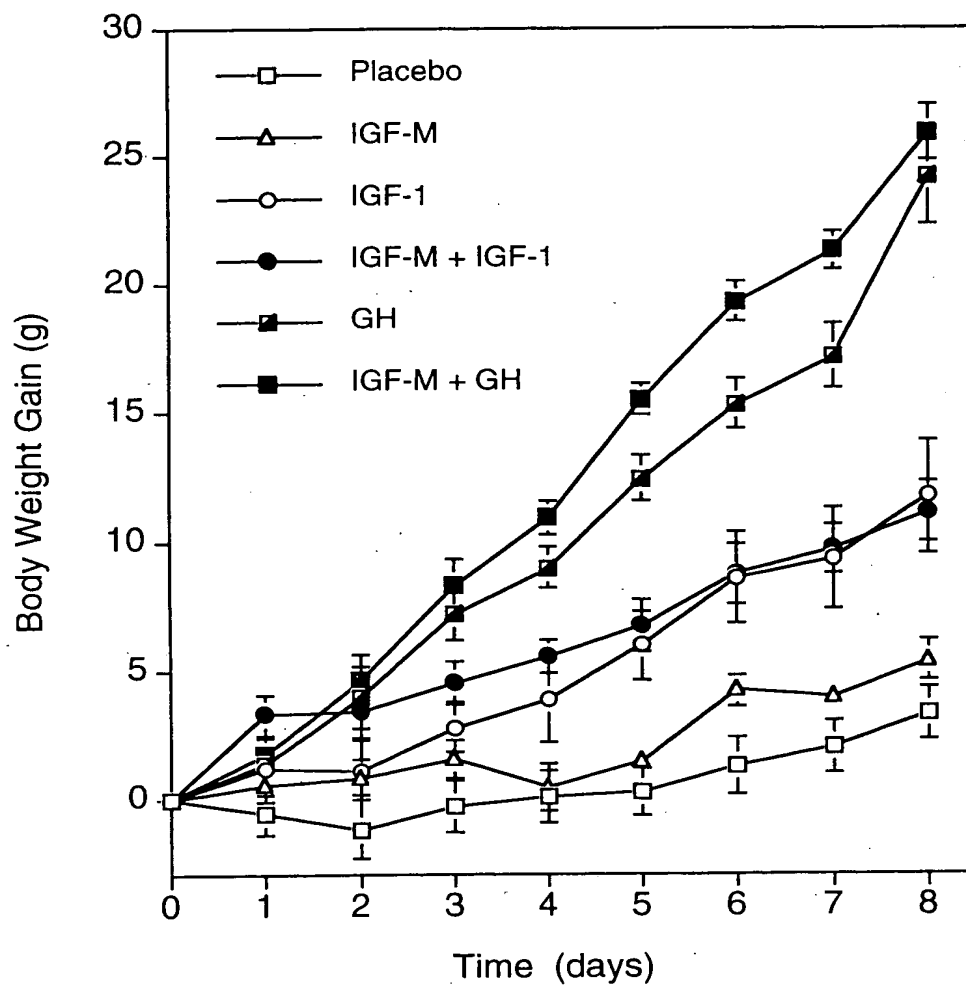
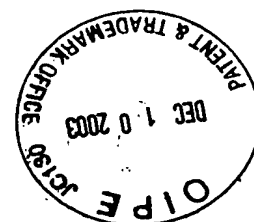


FIG. 18



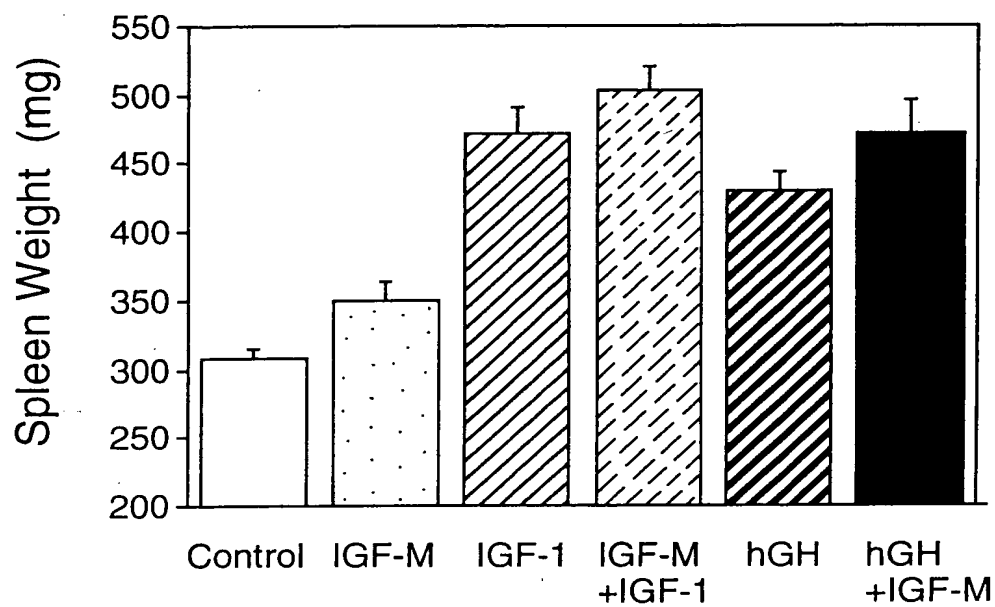


FIG. 19A

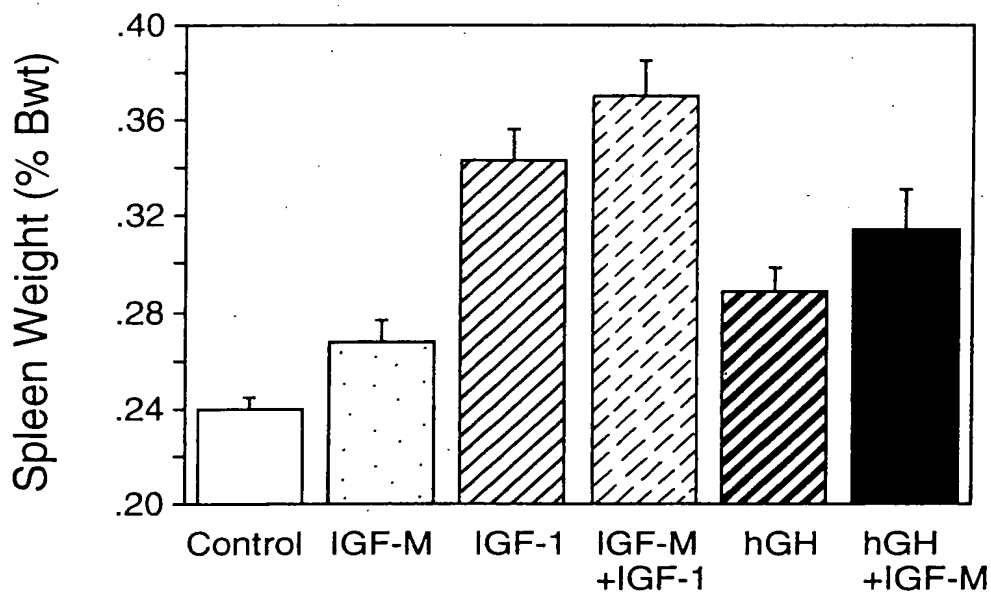
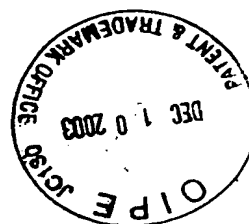


FIG. 19B



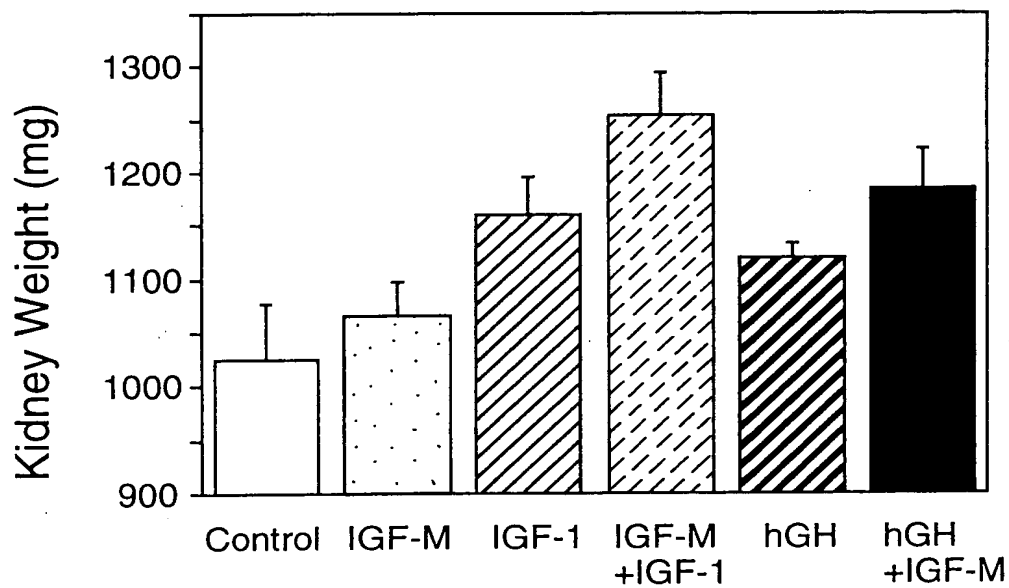


FIG. 20A

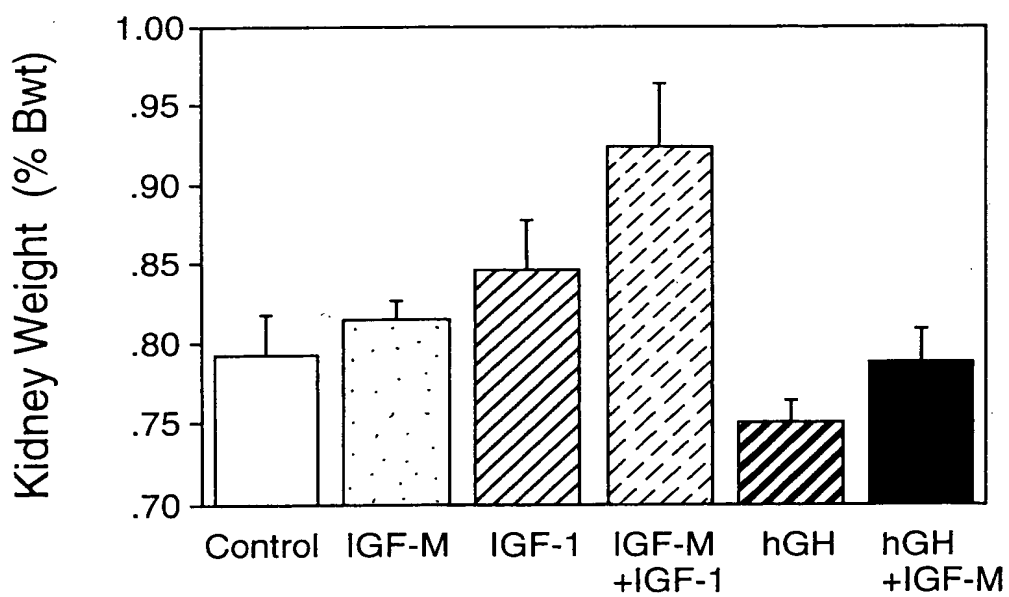
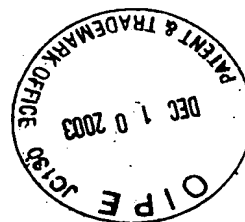


FIG. 20B



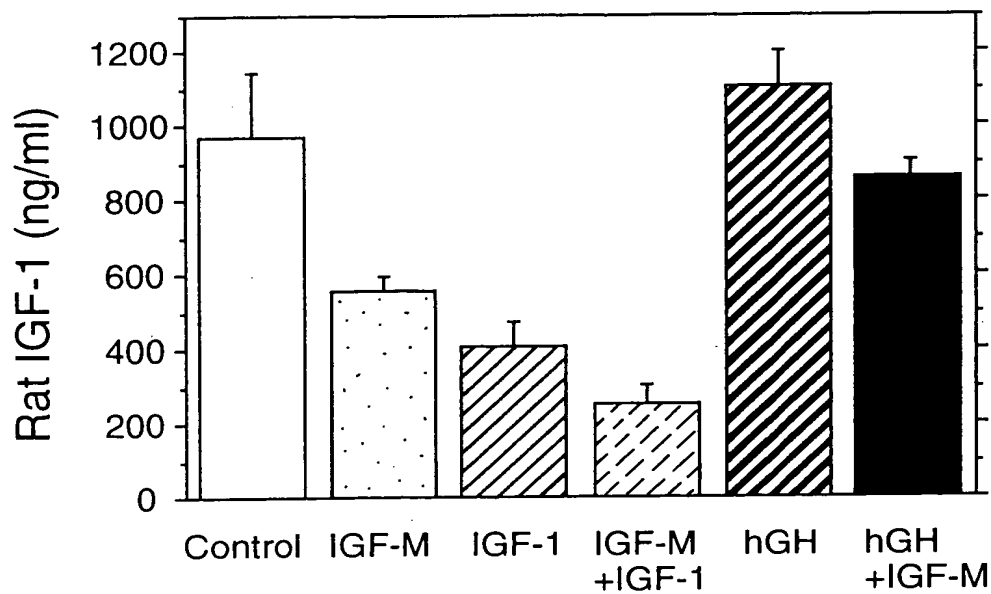


FIG. 21A

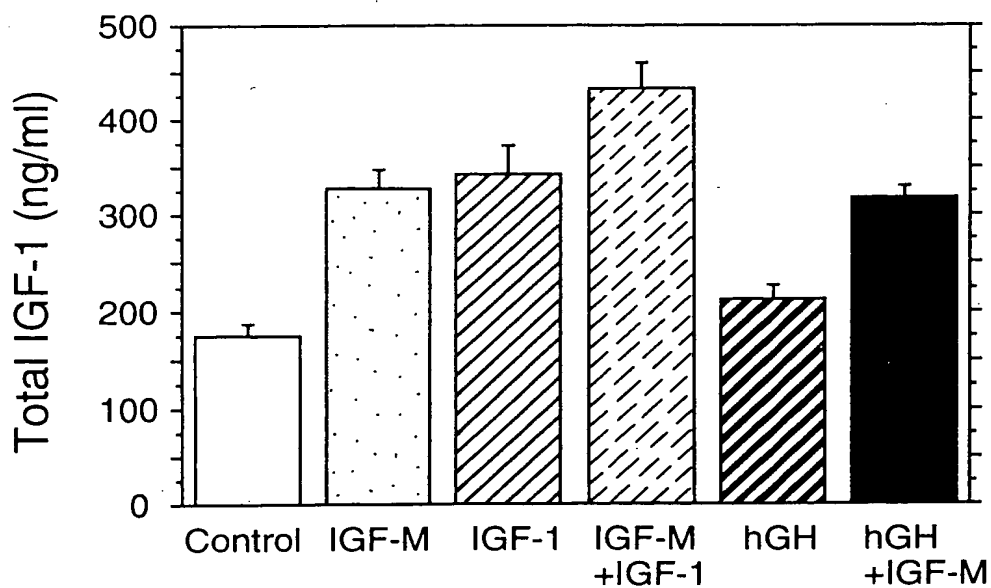
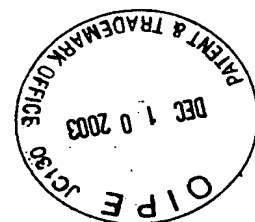


FIG. 21B



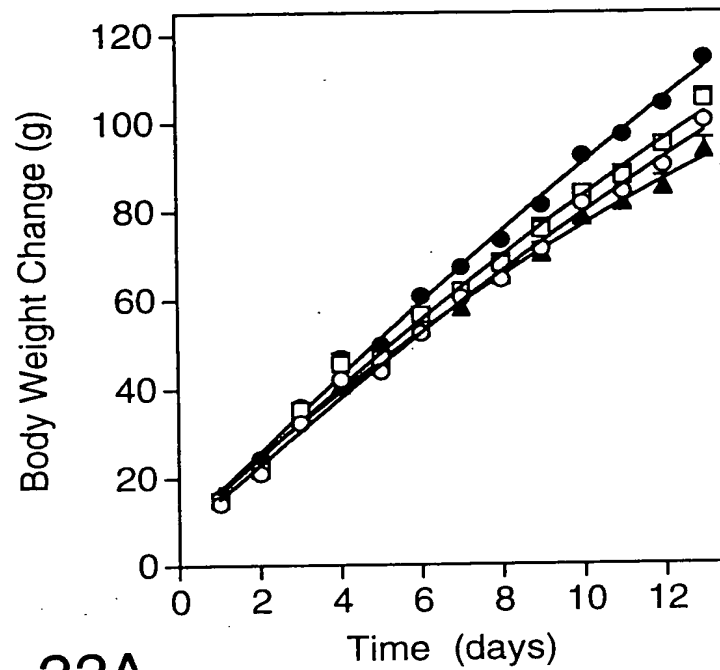


FIG. 22A

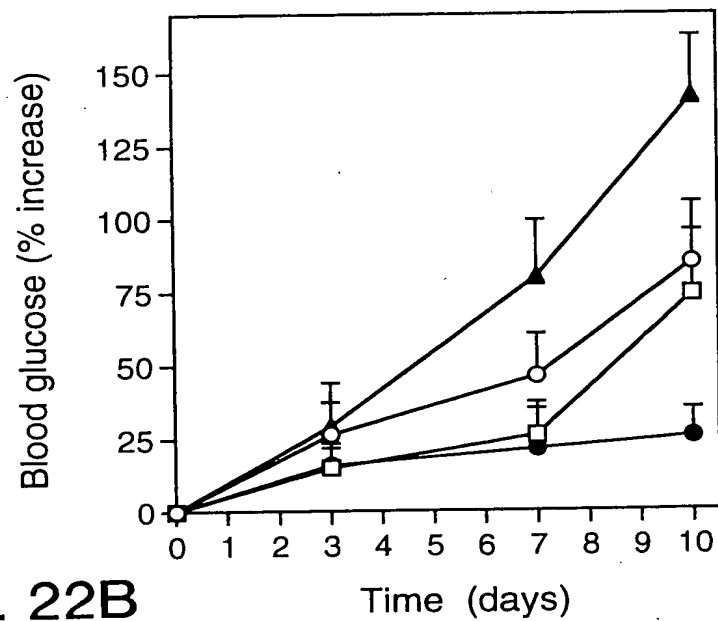


FIG. 22B

- | | |
|--------------------------------|---------------------------------|
| —●— IGF-1 (150 µg, tid) | —□— IGF Mutant (150 µg, tid) |
| —○— IGF Mutant (50 µg, tid) | —▲— Excipient Control |



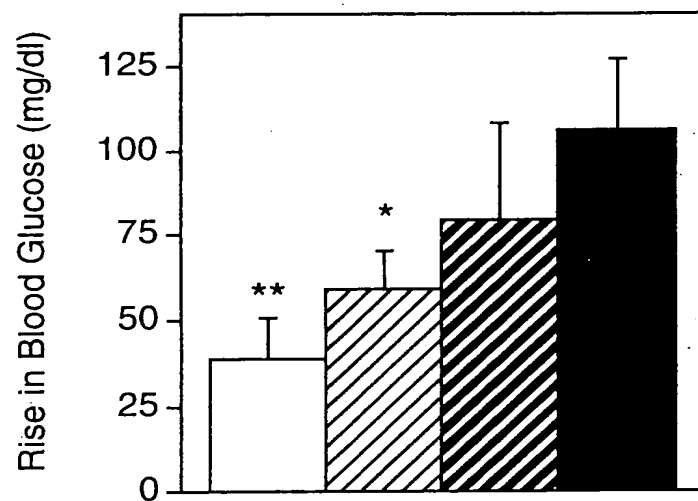


FIG. 23A

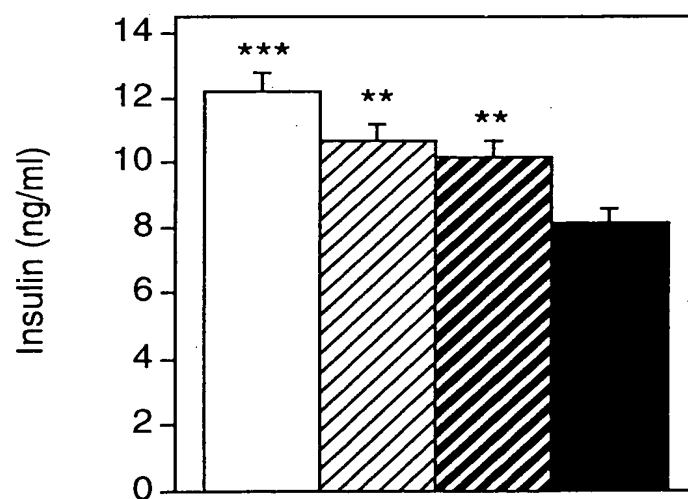
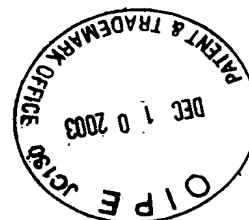


FIG. 23B

□ IGF-1 (150 µg, tid) ▨ IGF-Mutant (150 µg, tid)
 ▩ IGF-Mutant (50 µg, tid) ■ Control



plasmid t4.g8
length: 5140 (circular)

```
1 GAATTCAACT TCTCCATACT TTGGATAAGG AAATACAGAC ATGAAAAATC TCATTGCTGA GTTGTTATTT AAGCTTGCCC AAAAAGAAGA AGAGTCGAAT
CTTAAGTTGA AGAGGTATGA AACCTATTCC TTTATGTCTG TACTTTTAG AGTAACGACT CAACAATAAA TTTTCTTCTT TCTCAGCTTA

101 GAACCTGTG CGCAGGTAGA AGCTTTGGAG ATTATCGTCA CTGCAATGCT TCGCAATATG GGC AAAAATG ACCAACAGCG GTTGATTGAT CAGGTAGAGG
CTTGACACAC GCGTCCATCT TCGAAACCTC TAATAGCAGT GACGTTACGA AGCGTTATAC CGGTTTAC TGGTTGTGCG CAACATAACTA GTCCATCTCC

201 GGGCGCTGTA CGAGGTAAAG CCGATGCCA GCATTCCCTGA CGAGCATACG GAGCTGCTG GCGATTACGT AAAGAAGTTA TTGAAGCATC CTCGTCAGTA
CCCGGACAT GCTCCATTTC GGGCTACGGT CGTAAGGACT GTGCTATGC CTGACGAGC CGCTAATGCA TTTCTTCAAT AACTTCGTAG GAGCAGTCAT

301 AAAAGTTAAT CTTTTCACA GCTGTCATA AGTTGTCAG GCGGAGACTT ATAGTCGCTT TGT TTTTATT TTTTAATGTA TTTGTAAC TAACGCAAGT
TTTTCAATTA GAAAGTTGT CGACAGTATT TCAACAGTGC CCGCTCTGAA TATCAGCGAA ACAAAAATAA AAAATTACAT AACATTGAT CATGCGTTCA

401 TCACGTAAAA AGGGTATCTA GAGGTGAGG TGATTTTATG AAAAGAATA TCGCATTTCT TCTGCTATCT ATGTTCTGTT TTTCTATTGC TACAAATGCC
AGTGCATTTT TCCCATAGAT CTCCAACTCC ACTAAAATAC TTTTCTTAT AGCGTAAAGA AGAAGTAGA TACAAGCAA AAAGATAACG ATGTTACGG

501 TATGCATCTG GTACCGCCAT GGCTGATCCG AACCGTTTCC GCGGTAAAGA TCTGGCAGGT TCACCAAGGT GAGGATCCGG AGGAGCGCG GAGGTGACG
ATACGTAGAC CATGGCGGTA CCGACTAGGC TTGGCAAAG CGCCATTCT AGACCGTCCA AGTGGTCCAC CTCCTAGGCC TCCTCCGCG CTCCTACTGC

1 SerG lyThrAlaMe tAlaAspPro AsnArgPheA rgGlyLysAs pLeuAlaGly SerProGlyG lyGlySerG lYglyGlyAla GluGlyAspAsp

601 ATCCCGCAAA AGCGGCCTTT AACCTCCCTGC AACCTCCAGC GACCGAATAT ATCGGTTATG CGTGGGCGAT GGTGTTGTC ATTGTCGGCG CAACATATCGG
TAGGGCGGTT TCGCCGGAAA TTGAGGGACG TTCGGAGTCG CTGGCTTATA TAGCCAATAC GCACCCGCTA CCAACAACAG TAACAGCCGC GTTGATAGCC

33 ProAlaLy salaAlaPhe AsnSerLeuG lAlaSerAl aThrGluTyr lIeGlyTyrA laTrpAlaMe tValValVal lIeValGlyA laThrIleGly

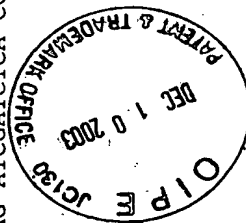
701 TATCAAGCTG TTTAAGAAAT TCACCTCGAA AGCAAGCTGA TAAACCGATA CAATTAAAGG CTCCTTTTGG AGCCTTTTTC TTTGGAGATT TTCAACGTGA
ATAGTTCGAC AAATTCCTTA AGTGGAGCTT TCGTTCGACT ATTTGGCTAT GTTAATTTC GAGGAAAACC TCGGAAAAAA AACCTCTAA AAGTTGCACT
66 lIeLysLeu PheLysLysP heThrSerLy salaSer

801 AAAAATTATT ATTGCAATT CCTTTAGTTG TTCCTTTCTA TTCTCACTCC GCTGAAACTG TTGAAAGTTG TTTAGCAAAA CCCCATACAG AAAATTCAAT
TTTTTAATAA TAAGCGTTAA GGAATCAAC AAGGAAAGAT AAGAGTGAGG CGACTTTGAC AACTTTCAAC AAATCGTTT GGGGTATGTC TTTAAGTAA

901 TACTAACGTC TGGAAAGACG ACAAACCTTT AGATCGTTAC GCTAACTATG AGGTTGTCT GTGGAATGCT ACAGCGTTG TAGTTTGTAC TGGTGACGAA
ATGATTGCAG ACCTTTCTGC TGTTTTCTGC TCTAGCAATG CGATTGATAC TCCCAACAGA CACCTTACGA TGTCGCAAC ATCAAAACATG ACCACTGCTT

1001 ACTCAGTGC TAGCTAGAGT GGGGTGGCT CTGGTCCGG TGATTTTGAT TATGAAAAGA TGGCAACCG TAATAAGGGG GCTATGACCG AAAATGCCGA
TGAGTCACAG ATCGATCTCA CCGCCACCGA GACCAAGGCC ACTAAAATA ATACTTTCT ACCGTTTGGG ATTTATCCCC CGATACTGGC TTTTACGGCT
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FIG. 24A



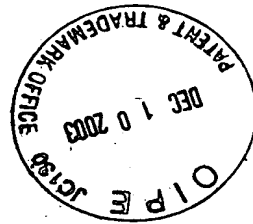
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ACTTTTGGCG GATGTCAGAC TGGGATTTCC GTTTGAAC TAAGACGGAT GACTAATGCC ACGACGATAG CTACCAAAGT AACCACTGCA AAGCCCGGAA
1201 GCTAATGGTA ATGGTGCTAC TGGTGATTTT GCTGGCTCTA ATTCCCAAAAT GGCTCAAGTC GGTGACGGTG ATAATTACCC TTTAATGAAT AATTCCGTC
CGATTACCAT TACCACGATG ACCACTAAAA CGACCGAGAT TAAGGTTTA CCGAGTTCAG CCAGTCCAC TATTAAGTGG AAATTACTTA TTAAAGGCAG
1301 AATAATTACC TTCCCTCCCT CAAATCGGTTG AATGTGCCCC TTTTGTCTTT AGCGCTGGTA AACCATATGA ATTTCTATT GATTGTGACA AAATAAACTT
TTATAAATGG AAGGGAGGA GTTAGCCAAC TTACAGCGGG AAAACAGAAA TCGCGACCAT TTGGTATACT TAAAAGATAA CTAACACTGT TTTATTTGAA
1401 ATTCCGTGGT GTCTTTGGT TTTCTTTTATA TGTGTCACC TTTTCTTAC TATTGCTAAC ATACTGCGTA ATAAGGAGTC TTAATCATGC
TAAGGCACCA CAGAAACGCA AAGAAAATAT ACAACGGTGG AATACATAC ATAAAAGATG CAAACGATG TATGACGCAT TATTCCTCAG AATTAGTAGC
3201 ACTCAAAGGC GGTAAATACG TTATCCACAG AATCAGGGA TAACGCAGGA AAGAACATGT GAGCAAAAGG CCAGCAAAAG GCCAGGAACC GTAAAAAGGC
TGAGTTTCCG CCATTATGCC AATAGGTGC TTAGTCCCTT ATGCGTCCCT TTTCTGTACA CTCGTTTCC GGTGCTTTTC CGGTCCCTTG CATTTTCCG
3301 CGCGTTGCTG GCGTTTTC ATAGGCTCCG CCCCCTGAC GAGCATCACA AAAATCGACG CTCAAGTCAG AGGTGGCGAA ACCCGACAGG ACTATAAAGA
GCGCAACGAC CGCAAAAAGG TATCCGAGG TATCCGAGG GGGGGGACTG CTCGTAGTGT TTTTAGCTGC GAGTTCAGTC TCCACCGCTT TGGGCTGTCC TGATATTTCT
3401 TACCAGGCGT TTCCCCCTGG AAGCTCCCTC GTGCGCTCTC CTGTTCCGAC CCTGCCGCTT ACCGGATACC TGTCCGCTCTT TCTCCCTTCG GGAAGCGTGG
ATGTTCCGCA AAGGGGAC TFCGAGGAG CACGCGAGAG GACAAGGCTG GAGCGGCGAA TGGCTATGG ACAGGCGGAA AGAGGGAAGC CCTTCGCACC
3501 CGCTTTCTCA TAGTCACG TGAGGTATC TCAGTTCGGT GTAGTTCGTT CGCTCCAAGC TGGGCTGTGT GCACGAACCC CCGGTTTCCG CCGACCGCTG
GCGAAAGAGT ATCGAGTGG ACATCCATAG AGTCAAGCCA CATCCAGCAA GCGAGGTTCC ACCCGACACA CGTGCTTGGG GGGCAAGTCG GCGTGGCGAC
3601 CGCCTTATCC GGTAACTATC GTCTTGAGTC CAACCCGGTA AGACACGACT TATGCCCACT TATGCCGTGA CCGTCCGTCCG TGACCATGT CCTAATCGTC TCGCTCCATA
GCGGAATAG CCATTGATAG CAGAACTCAG GTTGGGCCAT TCTGTGCTGA ATAGCGGTGA CCGTCCGTCCG TGACCATGT CCTAATCGTC TCGCTCCATA
3701 GTAGGCGGTG CTACAGAGTT CTTGAAGTGG TGGCTAACT ACGGCTACAC TAGAAGGACA GTATTGGTA TCTGCGCTCT GCTGAAGCCA GTTACCTTCG
CATCCGCCAC GATGTCTCAA GAATTCACC ACCGATTTGA TGCCGATGTG ATCTTCCTGT CATAAACCAT AGACGCGAGA CGACTTCGT CAATGGAAGC
3801 GAAAAAGAGT TGGTAGTCT TGATCCGGCA AACAAACCAC CGCTGGTAGC GGTGGTTTTT TTGTTTGCAA GCAGCAGATT ACGCGCAGAA AAAAAGGATC
CTTTTCTCTA ACCATCGAGA ACTAGGCCGT TTGTTGGTG GCGACCATCG CCACCAAAAA AACAAACGTT CGTCTGTCTAA TGGCGCTCTT TTTTCTCTAG
3901 TCAAGAAGAT CCTTTGATCT TTTCTACGG GTCTGACGCT CAGTGGAAAC AAAAACTCAG TTAAGGGATT TTGGTCTAGA GATTATCAA AAGGATCTTC
AGTCTTCTA GGAACCTAGA AAAGATGCCC CAGACTGCGA GTCACCTTGC TTTTGAAGTGC AATCCCTAA AACCACTACT CTAATAGTTT TTCTTAGAAG
4001 ACCTAGATCC TTTTAAATTA AAAATGAAGT TTTAAATCAA TCTAAAGTAT ATATGAGTAA ACTTGGTCTG ACAGTTTACCA ATGCTTAATC AGTGAGGCAC
TGGATCTAGG AAAATTTAAT TTTTACTTCA AAATTTAGTT AGATTTCATA TATACTCAT TGAACCCAGC TGTCAATGCT TACGAATTAG TCACTCCGTC

FIG. 24B



4101 CTATCTCAGC GATCTGTCTA TTTCTGTTTCAT CCATAGTTGC CTGACTCCCC GTCTGTGTAGA TAACTACGAT ACGGAGGGC TTACCATCTG GCCCCAGTGC
 GATAGAGTCG CTAGACAGAT AAAGCAAGTA GGTATCAACG GACTGAGGGG CAGCACATCT ATTGATGCTA TGCCCTCCCG AATGGTAGAC CGGGGTACAG
 4201 TGCAATGATA CCGCGAGACC CACGCTCACC GGCTCCAGAT TTATCAGCAA TAAACCAGCC AGCCGGAAGG GCGAGCGCA GAAGTGTGCC TGCAACTTTA
 ACGTTACTAT GCGCTCTGG GTGCGAGTGG CCGAGGTCTA AATAGTCGTT ATTTGGTCGG TCGGCTTCC CGGCTCGCGT CTTCCACCAGG ACGTTGAAAT
 4301 TCCGCCCTCCA TCCAGTCTAT TAAITGTTGC CGGGAAGCTA GAGTAAGTAG TTGCGCCAGTT AATAGTTTGC GCAACGTTGT TGCCATTGCT GCAGGCATCG
 AGGCGGAGGT AGGTCAGATA ATTAACAACG GCCCTTCGAT CTCAATTCATC AAGCGGTCAA TTATCAAAACG CGTTGCAACA ACGGTAACGA CGTCCGTAGC
 4401 TGGTGTACAG CTCGTCGTTT GGTATGGCTT CATTGAGCTC CGGTTCCCAA CGATCAAGGC GAGTTACATG ATCCCCCATG TTGTGCAAAA AAGCGGTTAG
 ACCACAGTGC GAGCAGCAAA CCATACCGAA GTAAGTCGAG GCCAAGGGTT GCTAGTTCCG CTCATGTAC TAGGGGGTAC AACACGTTTT TTCGCCAATC
 4501 CTCCTTCGGT CCTCCGATCG TTGTCAGAAG TAAGTTGGCC GCAGTGTTAT CACTCATGGT TATGGCAGCA CTGCATAATT CTCTTACTGT CATGCCATCC
 GAGGAAGCCA GGAGGCTAGC AACAGTCTTC ATTCAACCGG CGTCACAATA GTGAGTACCA ATACCGTCTG GACGTATTAA GAGAATGACA GTACGGTAGG
 4601 GTAAGATGCT TTTCTGTGAC TGGTGAGTAC TCAACCAAGT CATTCTGAGA ATAGTGTATG CCGCGACCGA GTTGCTCTTG CCCGGCGTCA ACACGGGATA
 CATTCTACGA AAAGACACTG ACCACTCATG AGTTGGTTCA GTAAGACTCT TATCACATAC GCCGCTGGCT CAACGAGAAC GGGCCGCGAGT TGTGCCCTAT
 4701 ATACCGCGCC ACATAGCAGA ACTTTAAAAG TGCTCATCAT TGGAAAACGT TCTTCGGGGC GAAAACCTCTC AAGGATCTTA CCGCTGTTGA GATCCAGTTC
 TATGGCGCGG TGTATCGTCT TGAAATTTTC ACGAGTAGTA ACCTTTTGCA AGAAGCCCCG CTTTTGAGAG TTCTAGAAAT GCGGACAACCT CTAGGTCAAG
 4801 GATGTAACCC ACTCGTGCAC CCAACTGATC TTCAGCATCT TTTACTTTCA CCAGCGTTTC TGGGTGAGCA AAAACAGGAA GGCAAAATGC CGCAAAAAAAG
 CTACATTGGG TGAGCACGTG GGTGACTAG AAGTCGTAGA AAATGAAAAGT GGTGCAAAAG ACCCACTCGT TTTTGTCTCTT CCGTTTTTACG GCGTTTTTTC
 4901 GGAATAAGGG CGACACGGAA ATGTTGAATA CTCATACTCT TCCTTTTTC ATATTATTGA AGCATTTATC AGGTTATTG TCTCATGAGC GGATACATAT
 CCTTATTCCC GCTGTGCTT TACAACCTAT GAGTATGAGA AGGAAAAAGT TATAATAACT TCGTAAATAG TCCCAATAAC AGAGTACTCG CCTATGTATA
 5001 TTGAATGTAT TTAGAAAAAT AAACAAATAG GGGTTCCGCG CACATTTCCT CGAAAAAGTGC CACCTGACGT CTAAGAAAAAC ATTATTATCA TGACATTAAC
 AACTTACATA AATCTTTTAA TTTGTTTATC CCCAAGGCGC GTGTAAAGGG GCTTTTCACG GTGGACTGCA GATTCTTTGG TAATAATAGT ACTGTAATTG
 5101 CTATAAAAAAT AGGCGGTATCA CGAGGCCCTT TCGTCTTCAA
 GATATTTTTA TCCGCATAGT GCTCCGGGAA AGCAGAAAGTT

FIG. 24C



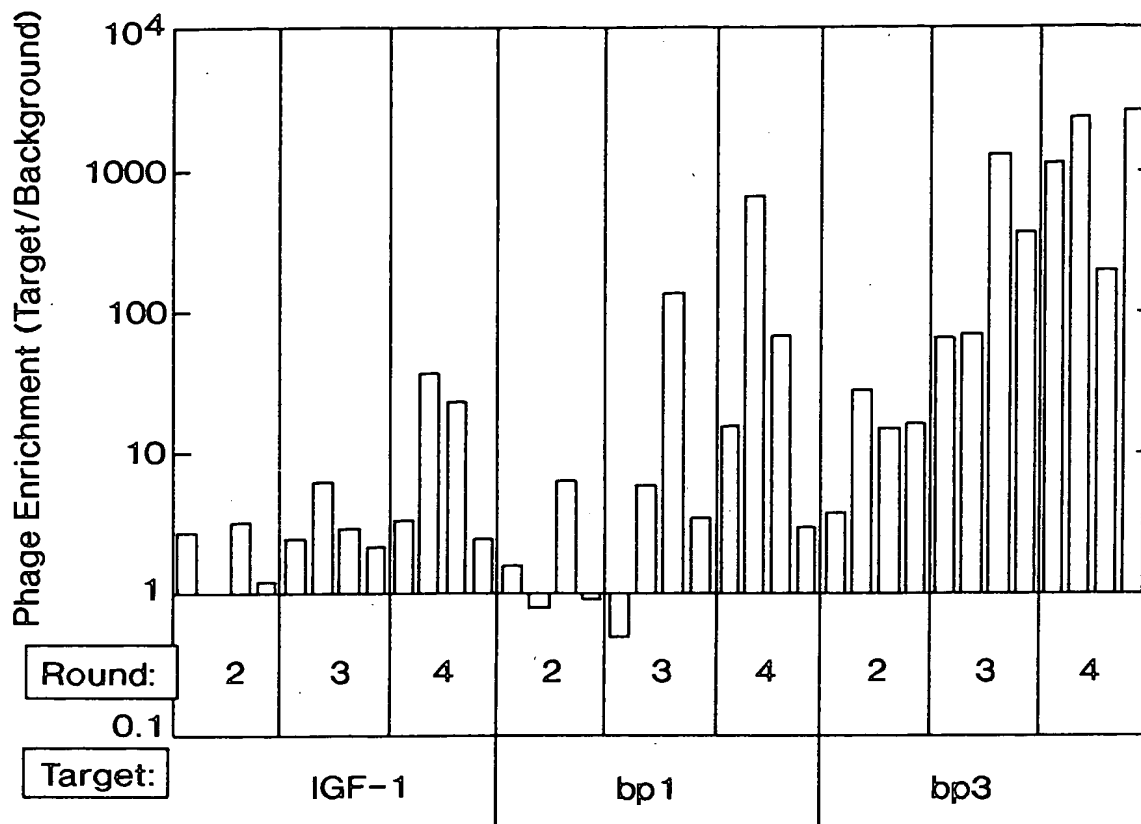


FIG. 25

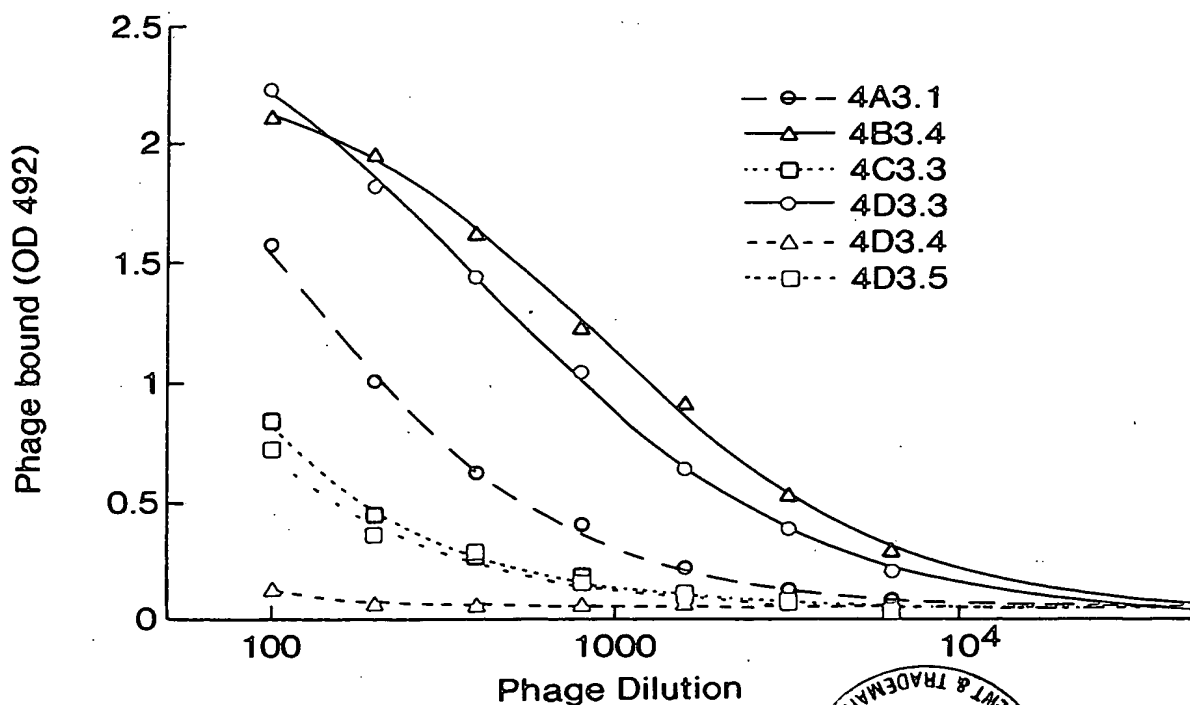


FIG. 26



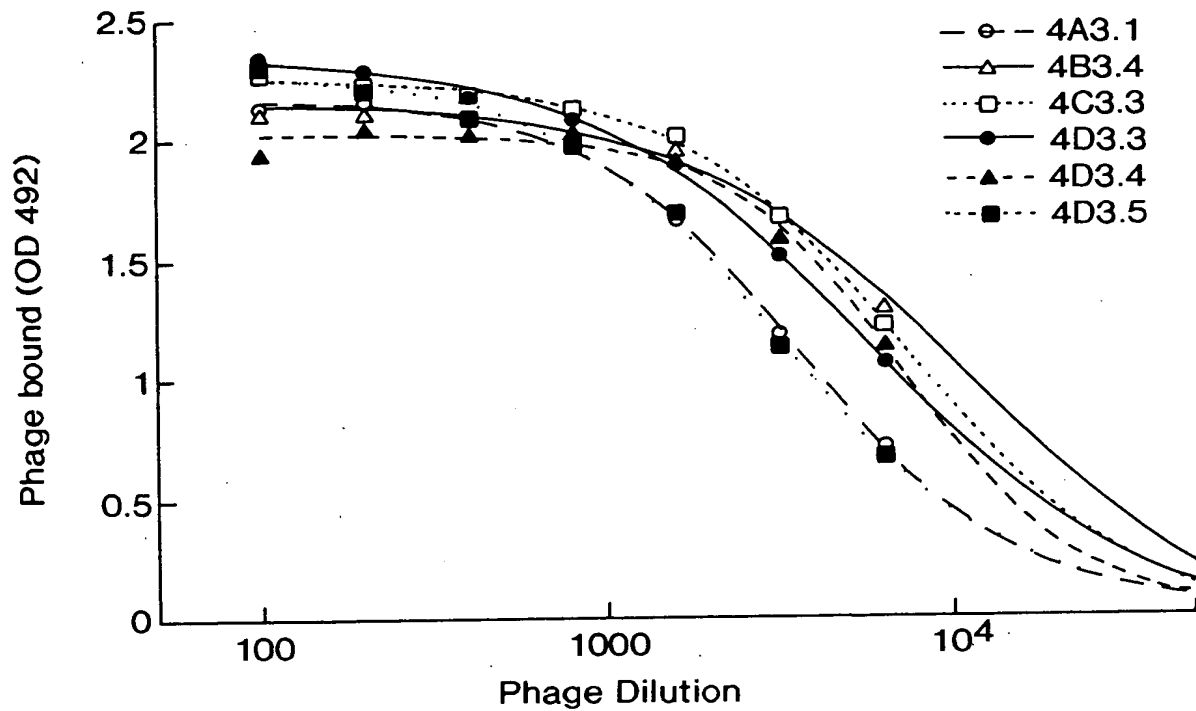


FIG. 27

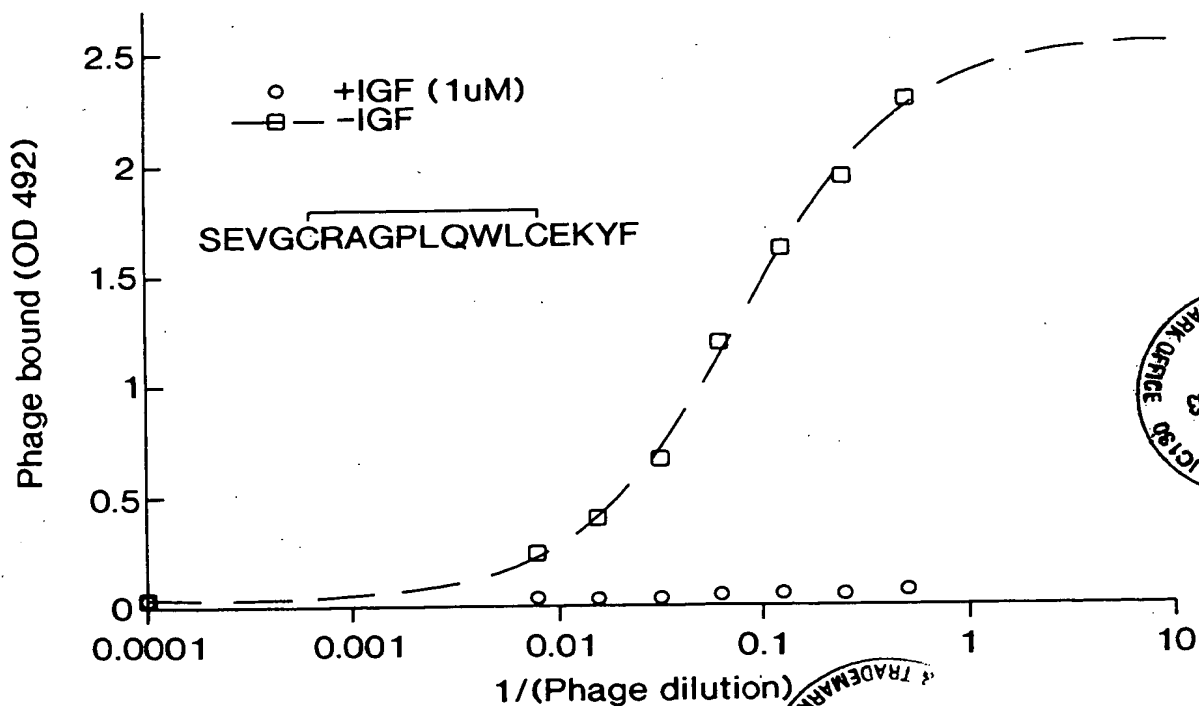
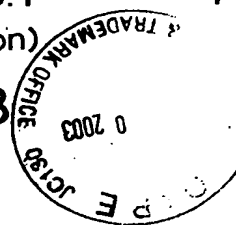
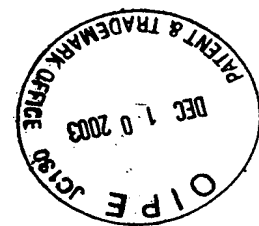


FIG. 28



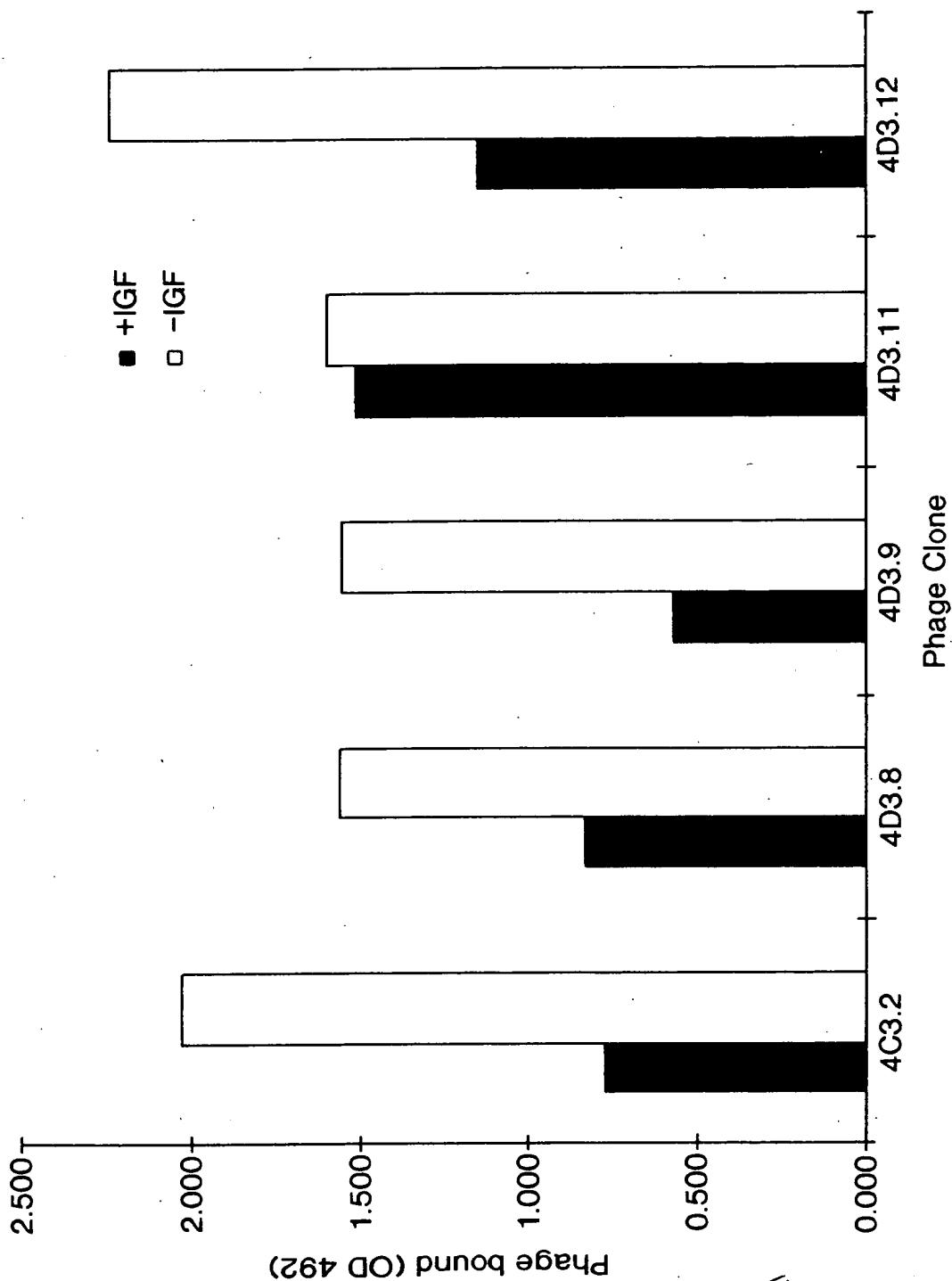
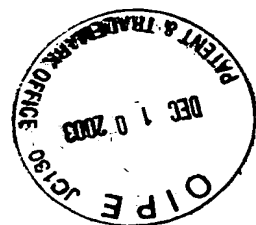
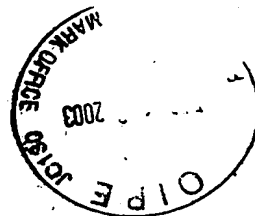
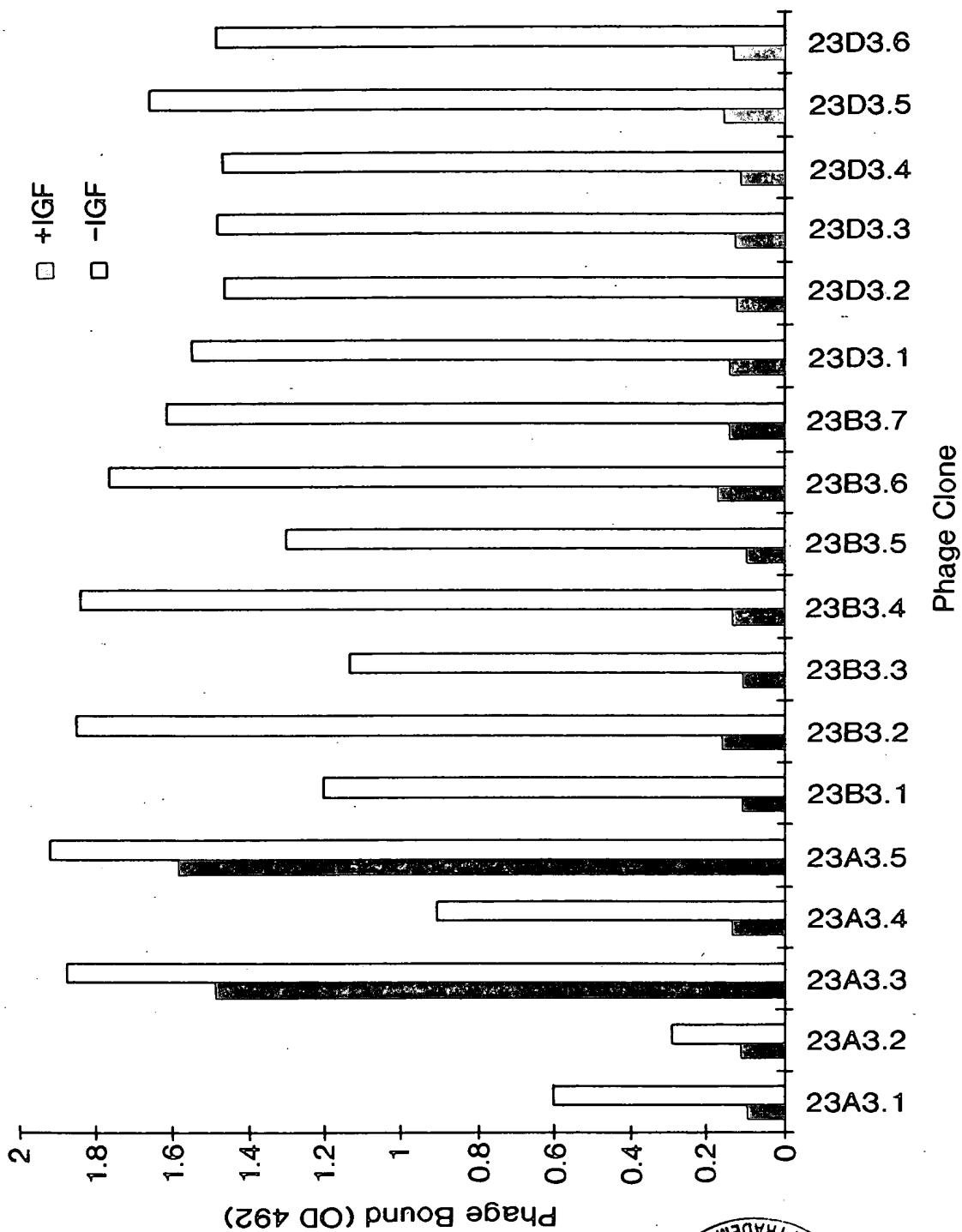


FIG. 29

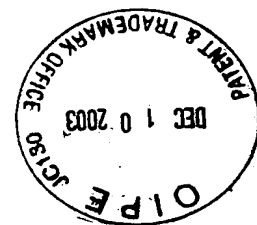
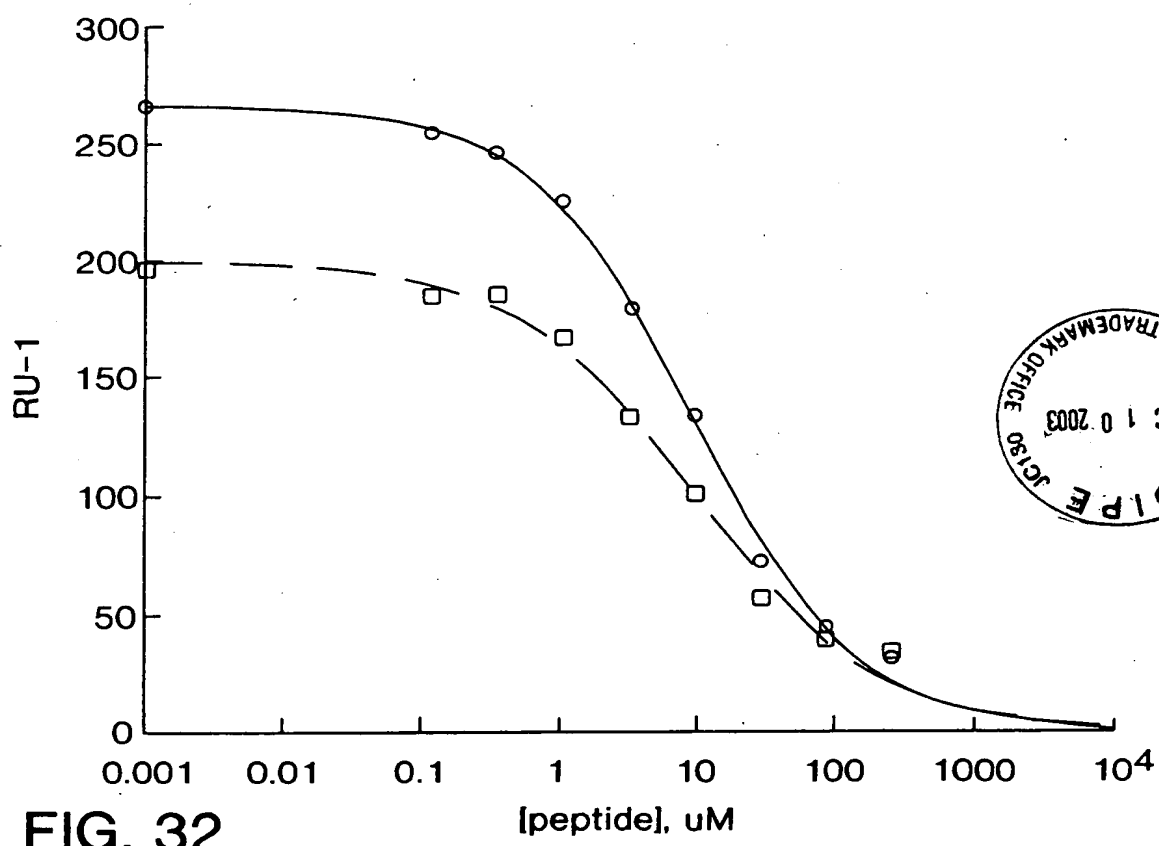
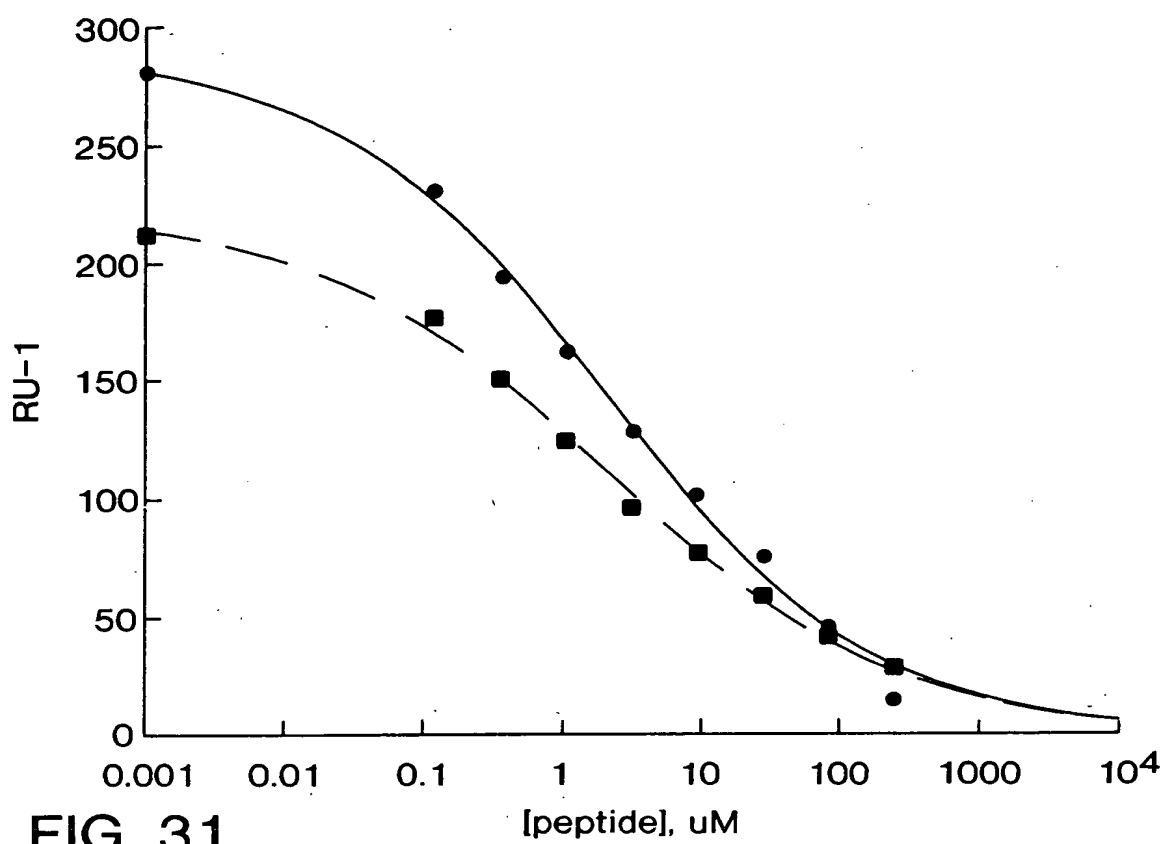




Phage Clone

FIG. 30





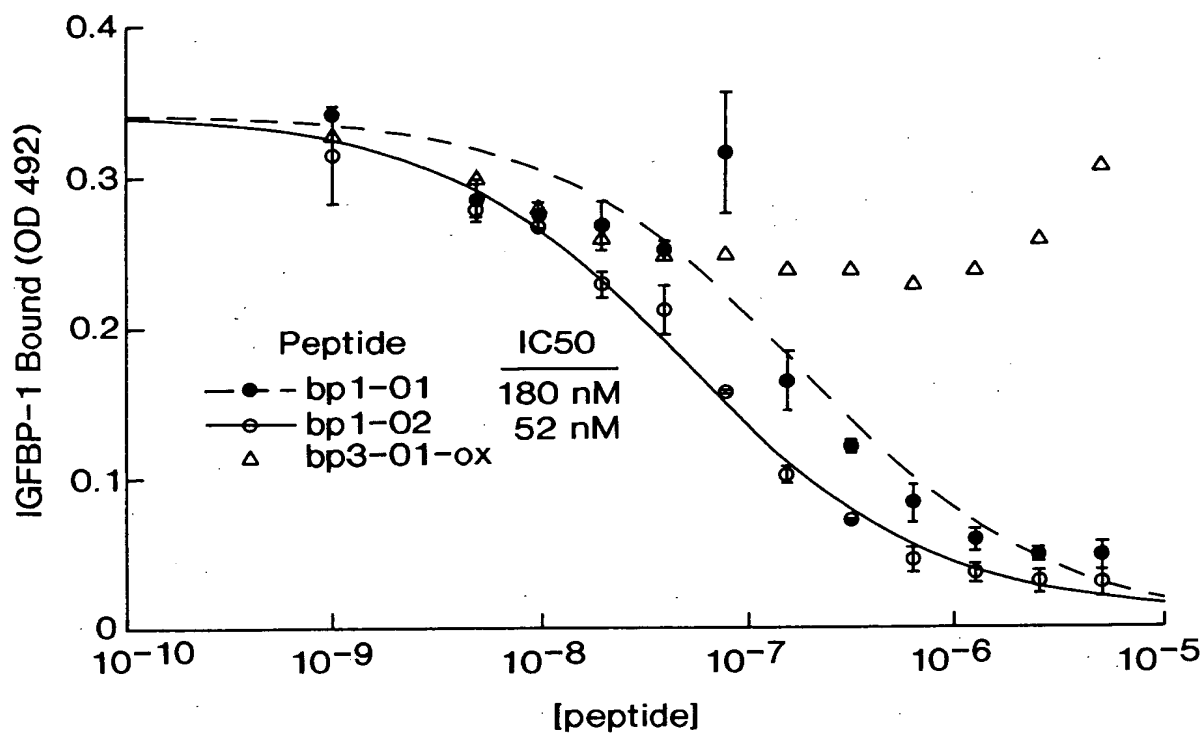


FIG. 33

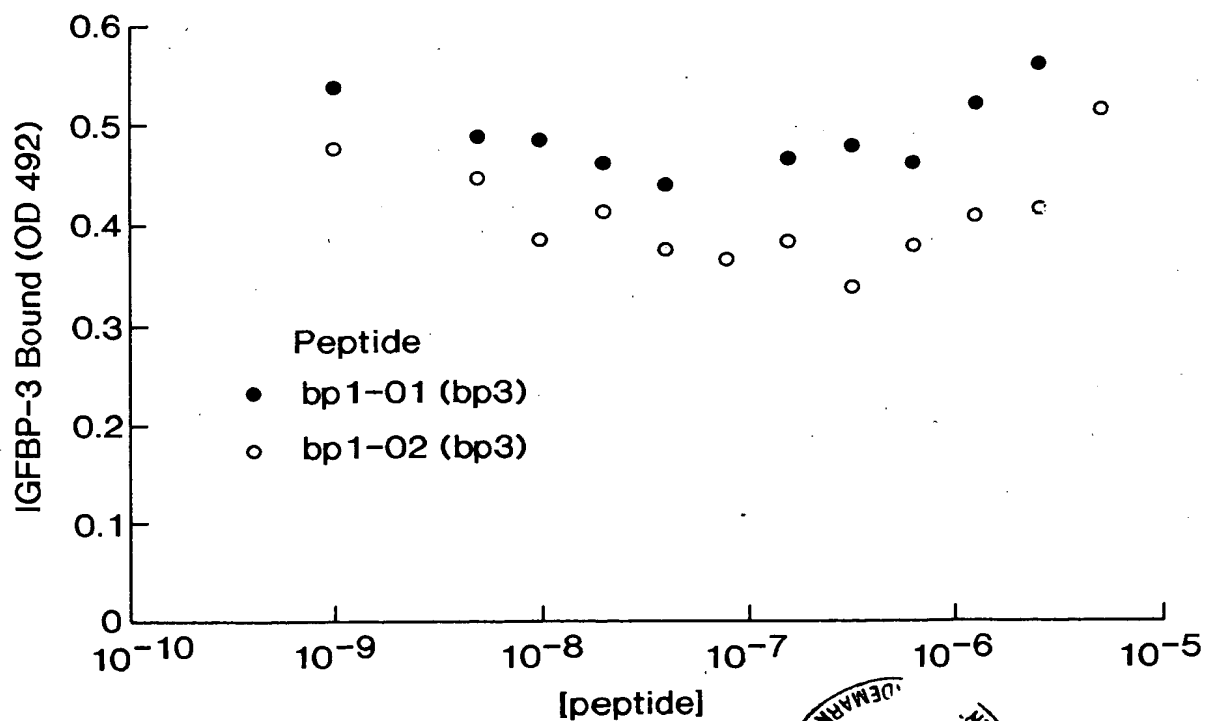
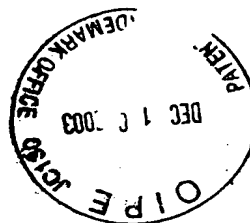


FIG. 34



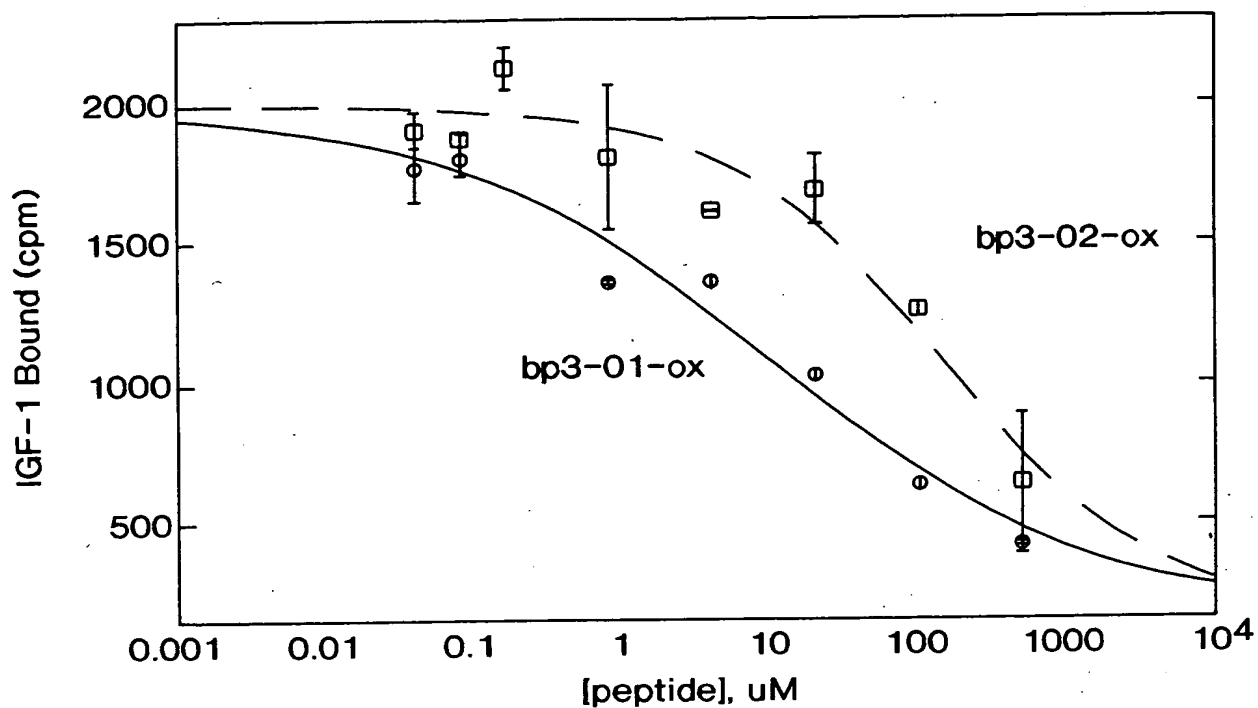


FIG. 35

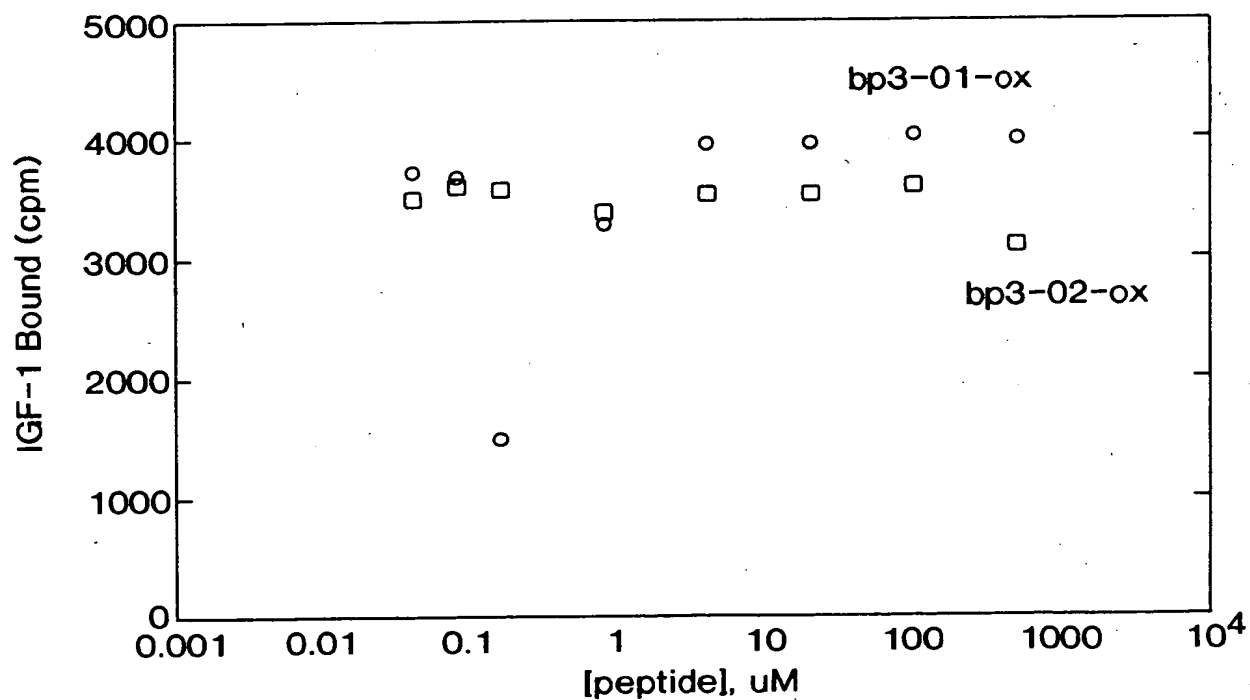


FIG. 36



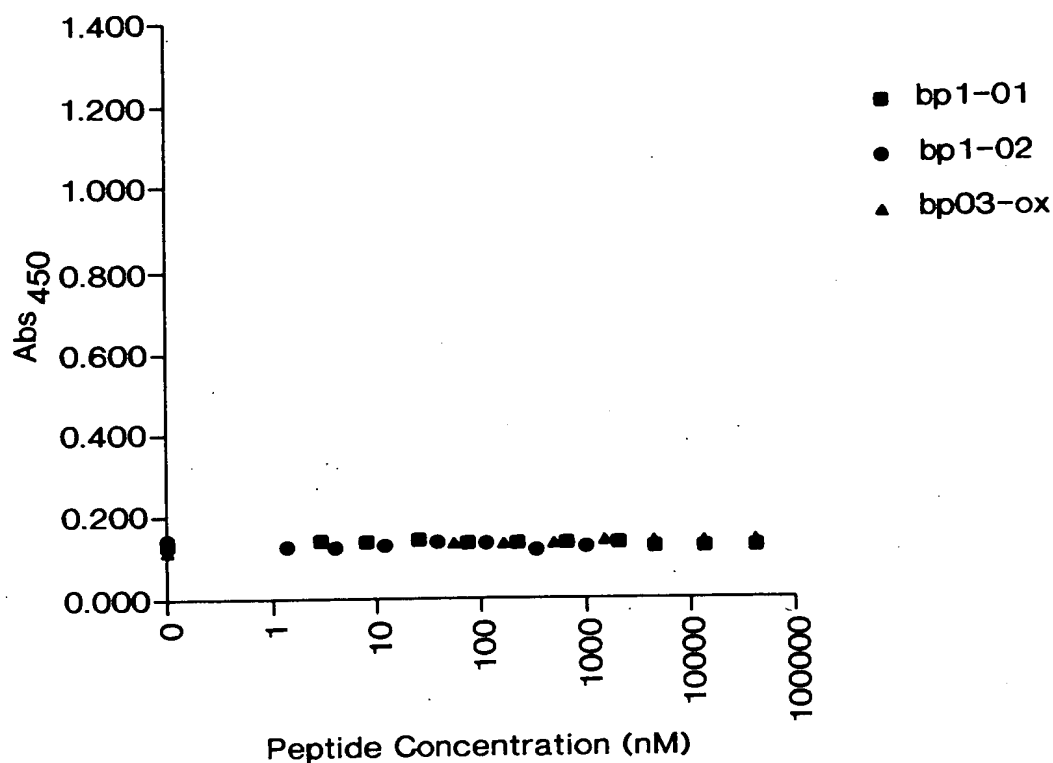


FIG. 37A

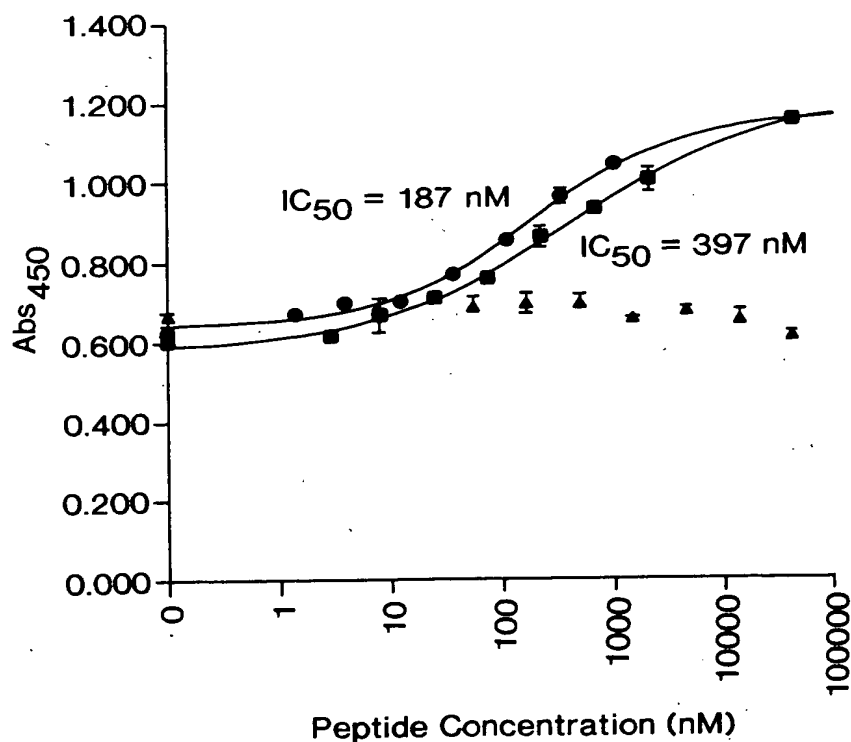
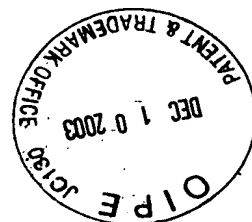


FIG. 37B



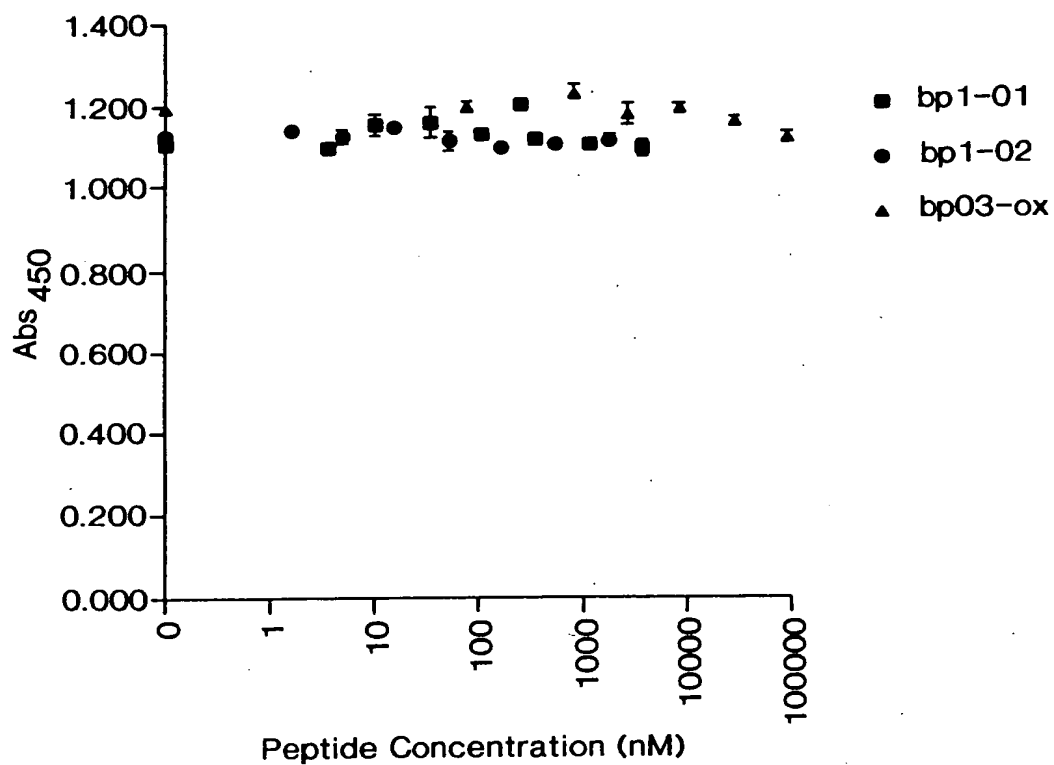


FIG. 37C

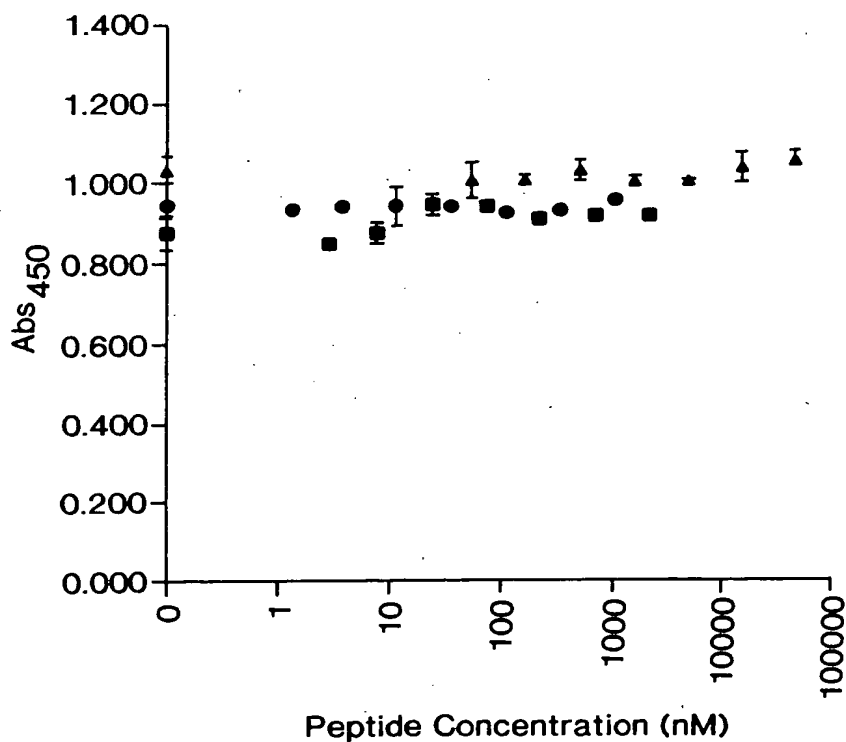
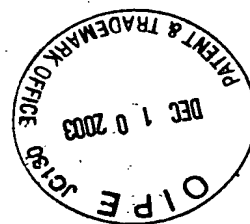


FIG. 37D



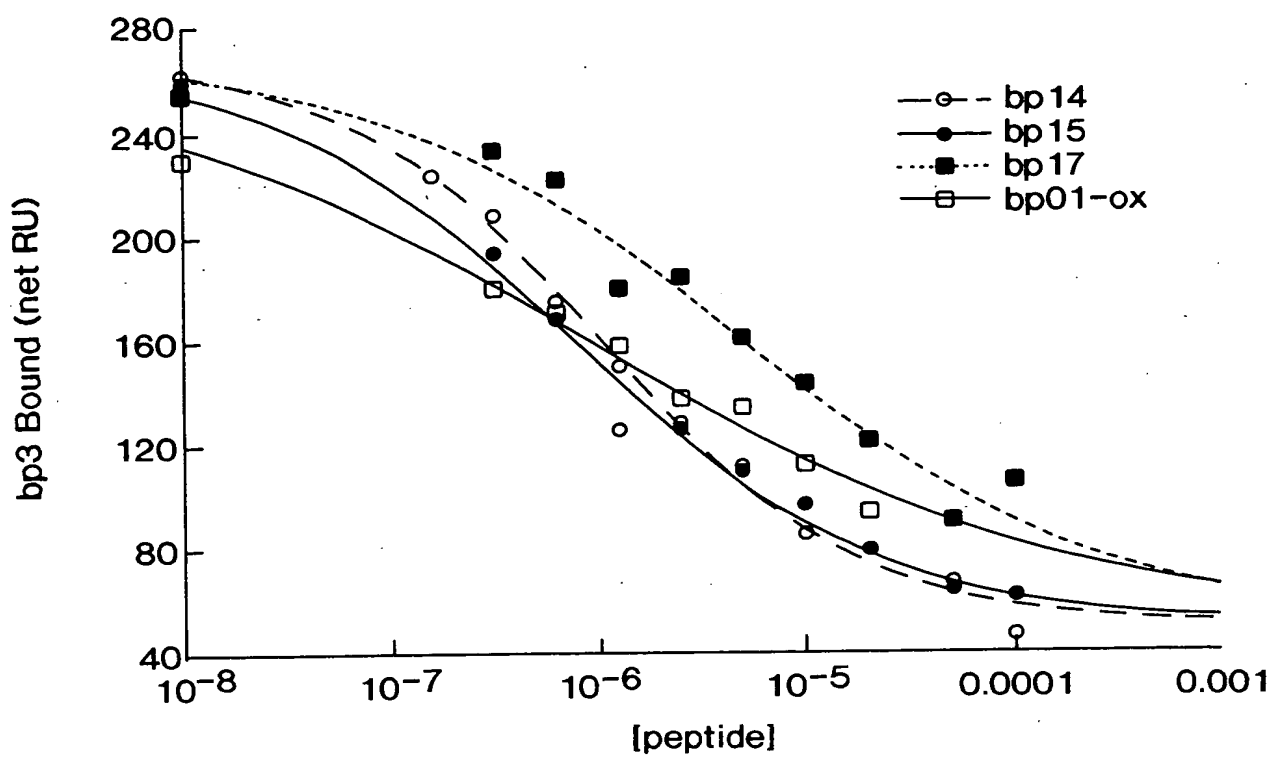


FIG. 38

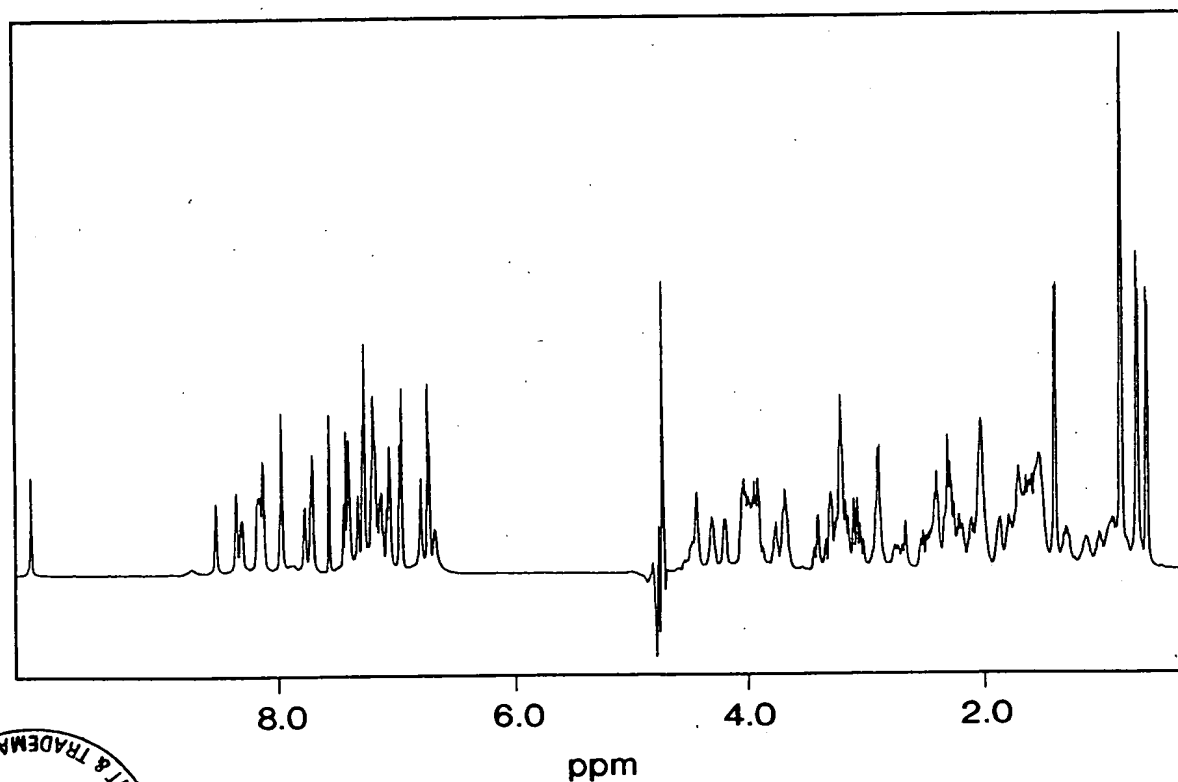


FIG. 39



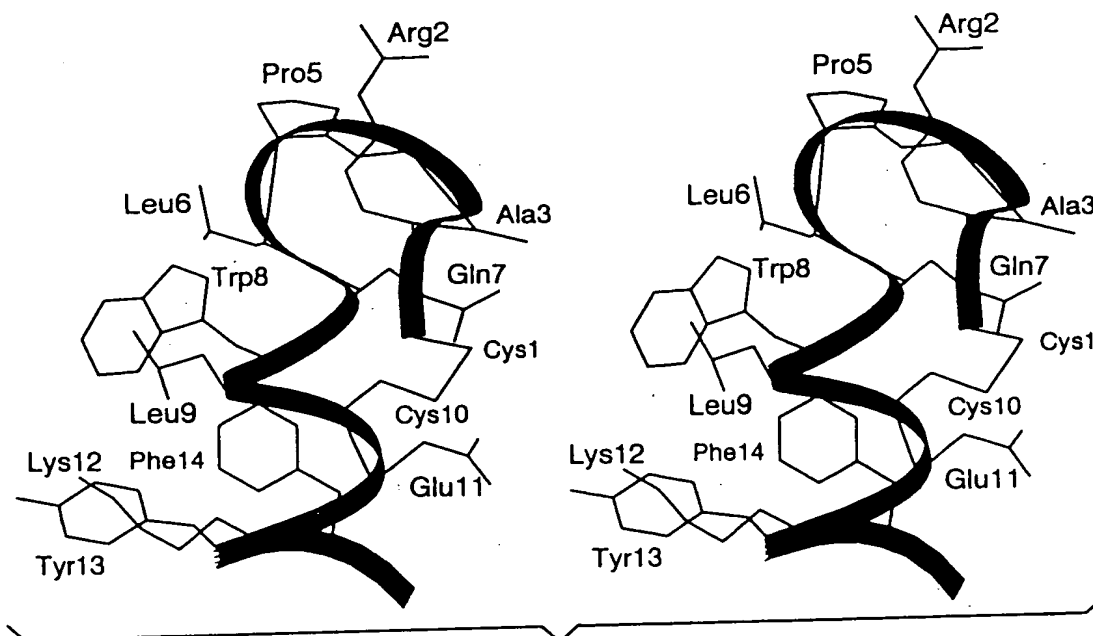


FIG. 40A

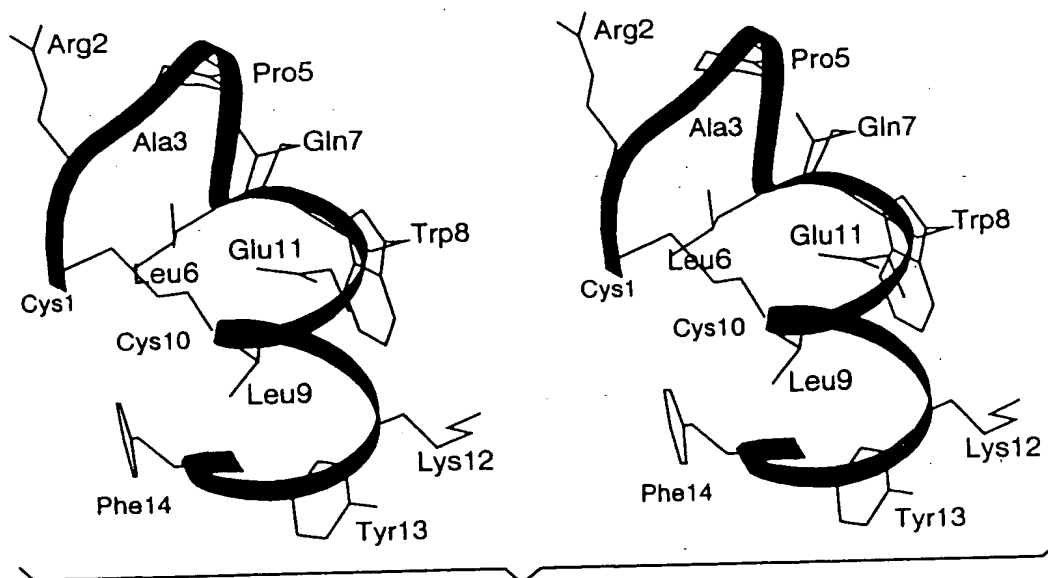


FIG. 40B



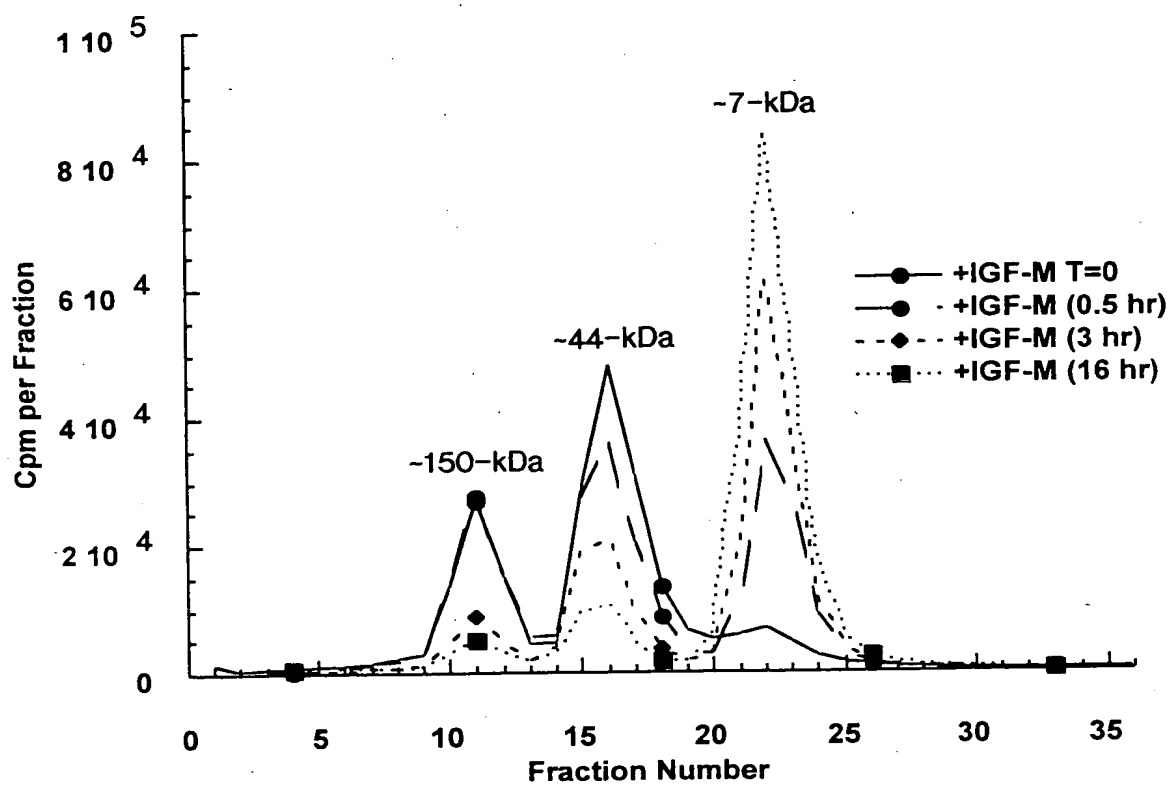
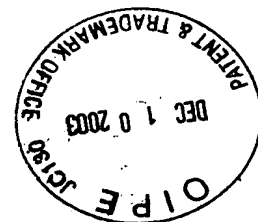
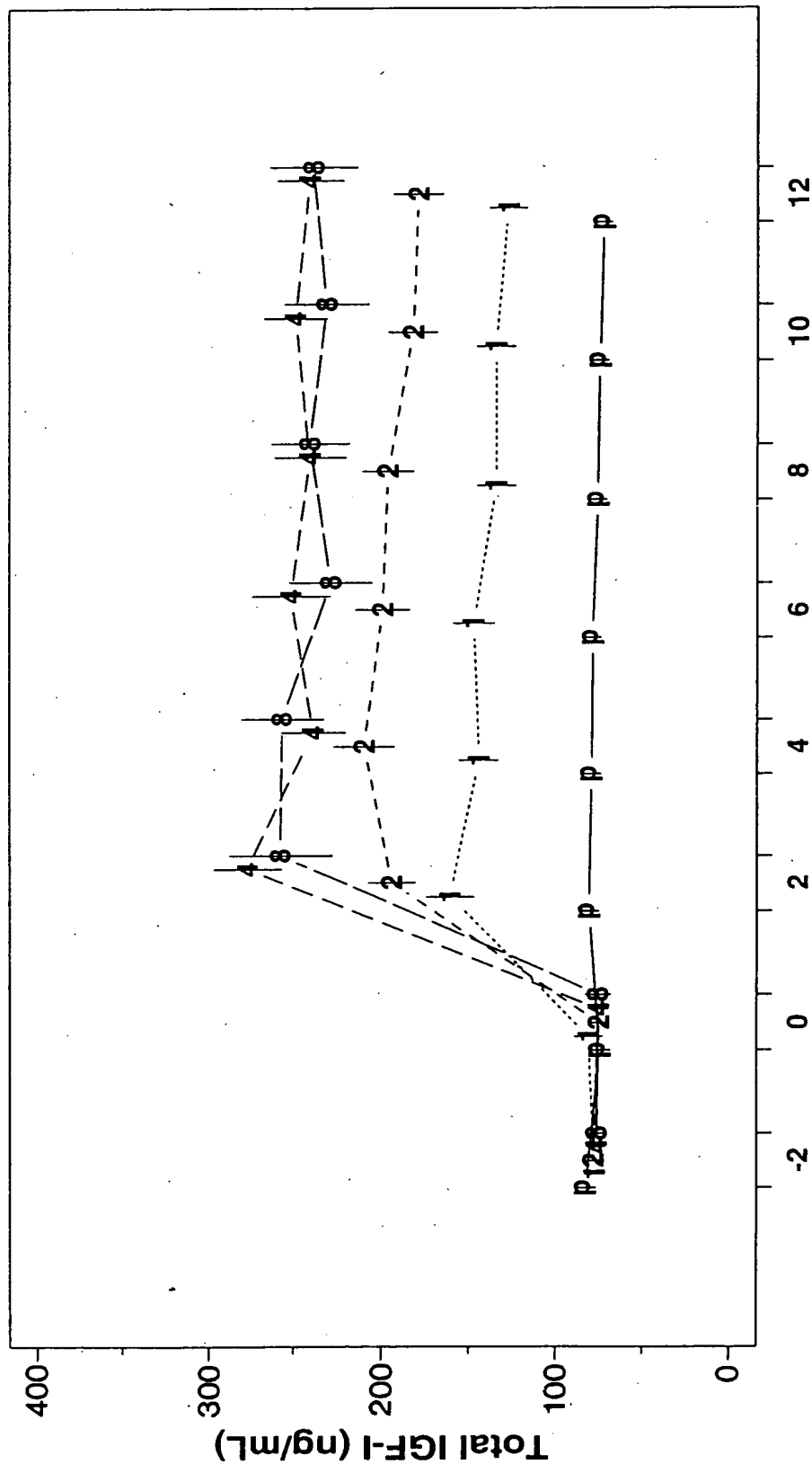


FIG. 41



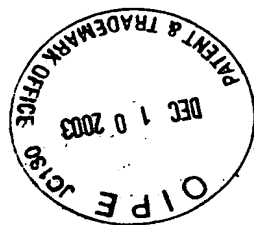
Effect of IGF-I Treatment on Total IGF-I

(Mean \pm SE)



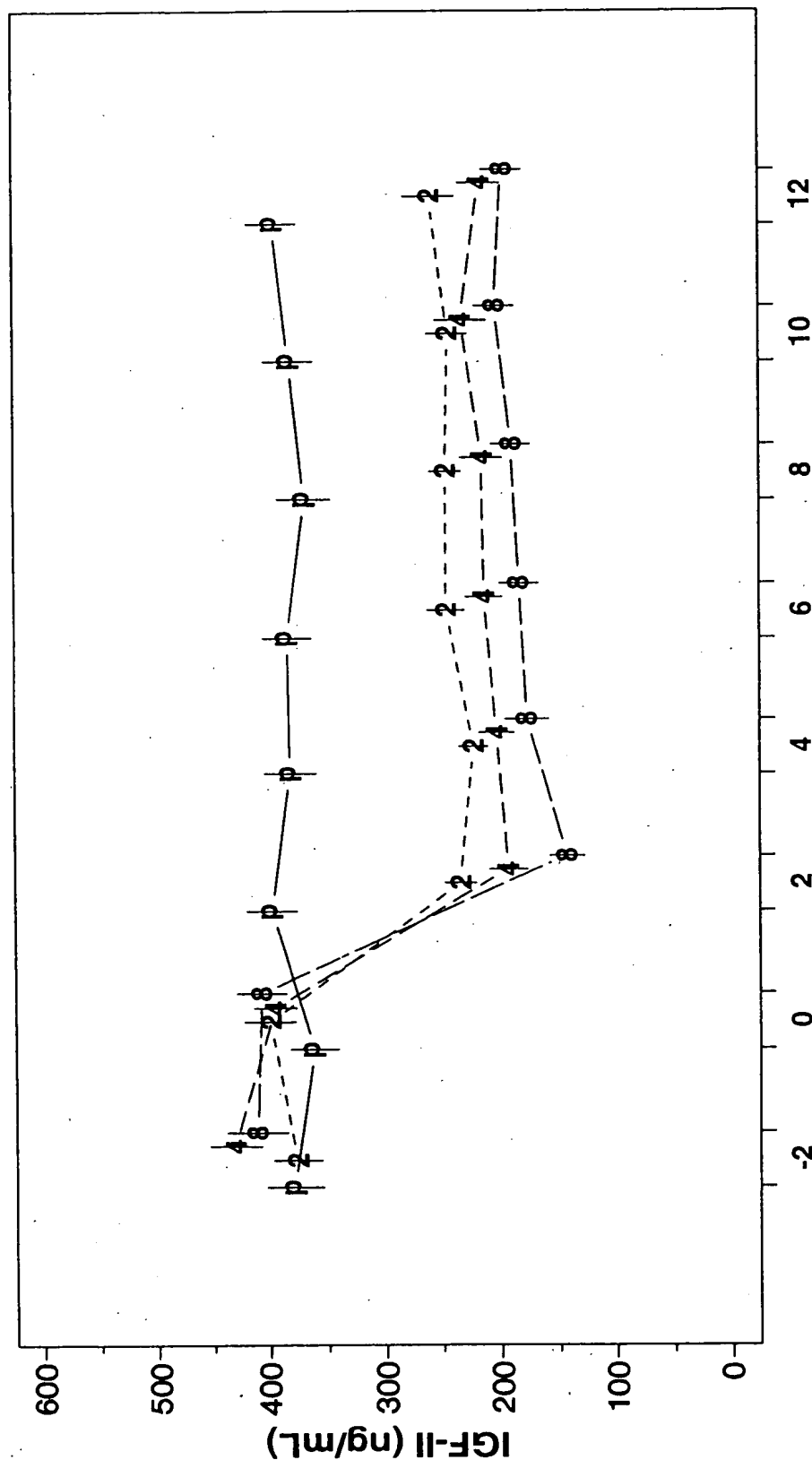
Treatment Visits (Week)

FIG. 42



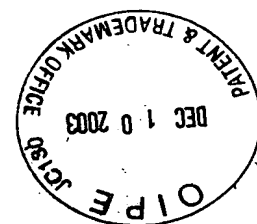
Effect of IGF-I Treatment on IGF-II

(Mean \pm SE)



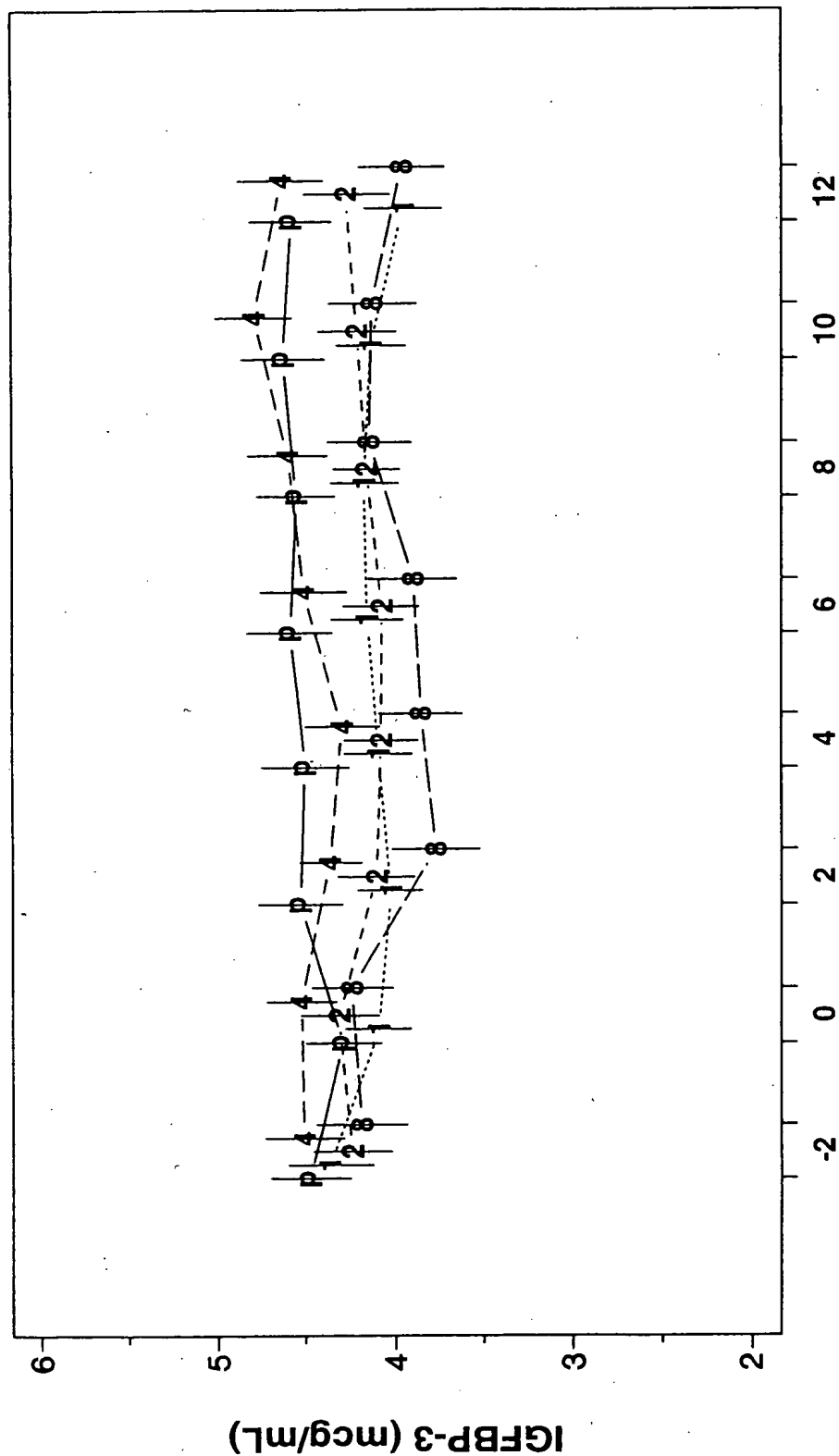
Treatment Visits (Week)

FIG. 43



Effect of IGF-I Treatment on IGFBP-3

(Mean \pm SE)



Treatment Visits (Week)

FIG. 44

